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<input type="checkbox"/>	L33	(williamson)adj(lorna)	1
<input type="checkbox"/>	L32	L31 and (CH2)adj(domain)	2
<input type="checkbox"/>	L31	(clark)adj(michael)	392
<input type="checkbox"/>	L30	(armour)adj(kathryn)	33
<input type="checkbox"/>	L29	L28 and (human)adj(IgG2)	10
<input type="checkbox"/>	L28	L27 and (human)adj(IgG4)	51
<input type="checkbox"/>	L27	L25 and (human)adj(IgG1)	126
<input type="checkbox"/>	L26	L25 and human IgG1	12503
<input type="checkbox"/>	L25	L24 and (CH2)adj(domain)	2219
<input type="checkbox"/>	L24	L23 and Fc	6484
<input type="checkbox"/>	L23	L22 and substitution	16865
<input type="checkbox"/>	L22	435/69.1.ccls.	22958
<input type="checkbox"/>	L21	L20 and (reduce)adj(effector)adj(function)	5
<input type="checkbox"/>	L20	424/133.1.ccls.	685
<input type="checkbox"/>	L19	L16 and 234V	0
<input type="checkbox"/>	L18	L16 and 233P	0
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<input type="checkbox"/>	L16	L15 and binding	45
<input type="checkbox"/>	L15	L14 and reduce	45
<input type="checkbox"/>	L14	L13 and (complement)adj(mediated)adj(lysis)	46
<input type="checkbox"/>	L13	L12 and (effector)adj(function)	667
<input type="checkbox"/>	L12	L11 and (CH2)adj(domain)	824
<input type="checkbox"/>	L11	L10 and chimeric	5833
<input type="checkbox"/>	L10	530/387.3-391.9.ccls.	12284
<input type="checkbox"/>	L9	L8 and (human)adj(IgG4)	19
<input type="checkbox"/>	L8	L5 and (human)adj(IgG1)	63
<input type="checkbox"/>	L7	L5 and human IgG1	12436
<input type="checkbox"/>	L6	L5 and 233.2.40	0
<input type="checkbox"/>	L5	L4 and reduce	105
<input type="checkbox"/>	L4	L3 and (complement)adj(mediated)adj(lysis)	107
<input type="checkbox"/>	L3	L2 and (CH2)adj(domain)	3008

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L2 ANSWER 1 OF 36 MEDLINE on STN  
1998400227. PubMed ID: 9731501. Chimeric human-mouse IgG antibodies with shuffled constant region exons demonstrate that multiple domains contribute to in vivo half-life. Zuckier L S; Chang C J; Scharff M D; Morrison S L. (Department of Nuclear Medicine, Albert Einstein College of Medicine, Bronx, New York 10461, USA. ) Cancer research, (1998 Sep 1) 58 (17) 3905-8. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Structural features that determine the differing rates of immunoglobulin catabolism are of great relevance to the engineering of immunologically active reagents. Sequences in the CH2 and CH3 region of IgG have been shown to regulate the rate of clearance through their interaction with FcRn. In an attempt to probe additional structural features that regulate antibody half-life, we have investigated two families of **chimeric antibodies**, composed of identical murine heavy and light antidansyl variable regions joined to human kappa light-chains and wild-type or shuffled human IgG heavy-chain constant regions. These antibodies were iodinated, and their clearance was studied in severe combined immunodeficient mice hosts by whole-body radioactivity measurements. Clearances of the wild-type and recombinant antibodies were

biphasic. In a panel of immunoglobulins derived from IgG2 and IgG3, as successive domains were varied from gamma2 to gamma3, beta-phase half-life gradually decreased from 337.0 h to 70.6 h. Statistical analysis suggested that the composition of each of the three domains affected half-life, and no single region of the molecule by itself determined the rate of clearance. In the second panel of immunoglobulins derived from IgG1 and IgG4, the construct with the amino terminus portion of the molecule derived from IgG4, joined within the **CH2 domain** to the COOH terminus portion of IgG1, had a half-life paradoxically greater than either IgG1, or IgG4 ( $P < 0.012$ ). All four IgG1/IgG4 constructs demonstrated presence of the concentration catabolism phenomenon, which is a unique hallmark of immunoglobulin catabolism. The contribution of all three constant region domains to immunoglobulin half-life may be due to distant conformational effects in addition to direct binding to protective receptors, and emphasizes the importance of distant sequences on the rate of immunoglobulin catabolism. Interesting possibilities regarding mechanisms controlling immunoglobulin metabolism are raised by the hybrid gamma4/gamma1 molecule with a half-life greater than either parental immunoglobulin. Understanding the relationships between the structure of these molecules and their clearance rate will further our ability to produce immunoglobulins with improved pharmacokinetic properties.

L2 ANSWER 2 OF 36 MEDLINE on STN

95111520. PubMed ID: 7529083. Construction and purification of domain-deleted immunoglobulin variants of the recombinant/chimeric B72.3 (y1) monoclonal antibody. Calvo B; Kashmiri S V; Hutzell P; Hand P H; Slavin-Chiorini D C; Schlom J; Zaremba S. (Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892. ) Cancer bioterapy, (1993 Spring) 8 (1) 95-109. Journal code: 9314021. ISSN: 1062-8401. Pub. country: United States. Language: English.

AB **Chimeric antibodies** have been produced against a pancarcinomic tumor associated antigen, TAG-72, by fusing the genes for the variable region of mouse MAb B72.3 to the genes for the constant region of human IgG. In our efforts to optimize the pharmacokinetics of plasma clearance and the efficiency of tumor localization and penetrance of cB72.3, we have now developed truncated versions of immunoglobulin heavy chains. The domain-deleted antibodies are produced by transfecting cells that produce chimeric kappa chains with expression vectors that encode chimeric heavy chains lacking the sequences that encode the **CH2 domain**, CH3 domain, or both. Despite the absence of these domains, the transfectomas secrete H2L2 tetramers with appropriate antigenic specificity. All the domain-deleted immunoglobulins can be purified by chromatography on Protein G Sepharose which binds to a site on the Fab region that is retained in the domain-deleted antibodies. The CH2CH3 domain-deleted immunoglobulin produced in cell culture is analogous in size to enzymatically produced F(ab')<sub>2</sub>.

L2 ANSWER 3 OF 36 MEDLINE on STN

93155484. PubMed ID: 7679128. Epitope mapping of human immunoglobulin-specific murine monoclonal antibodies with domain-switched, deleted and point-mutated **chimeric antibodies**. Hamilton R G; Morrison S L. (Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21224. ) Journal of immunological methods, (1993 Jan 14) 158 (1) 107-22. Journal code: 1305440. ISSN: 0022-1759. Pub. country: Netherlands. Language: English.

AB 27 engineered **chimeric antibodies** possessing human gamma, epsilon, mu or alpha constant regions and V region specificity for nitrophenyl or dansyl were used to study the isotype specificity of 29 murine monoclonal antibodies (MAbs) specific for human immunoglobulins (IgG1-4, IgE, IgM, IgA or secretory piece). The isotype-restricted immunoreactivity observed with wild-type **chimeric**

**antibodies** paralleled the pattern of each MAb's reactivity with purified human myeloma proteins. 16 mutant IgG anti-dansyl **chimeric antibodies** with genetically engineered domain switches, deletions or point-mutations were used as antigens to further characterize the epitopes recognized by the human IgG subclass-specific MABs. The binding of three human IgG1-specific MABs (HP6069, HP6070 and HP6091) was mapped to similar epitopes on the **CH2 domain** of human IgG1. Of the two anti-human IgG2 MABs tested, HP6002 reacted with the CH2 of IgG2 while HP6014 bound to the CH1 domain. Both anti-human IgG3 MABs (HP6047, HP6050) reacted with different regions of the IgG3 hinge. The anti-human IgG4 MABs (HP6023, HP6025) bound to a similar epitope on the carboxyl terminus of CH2 or the CH3 of human IgG4. The three exclusion antibodies (HP6019, HP6030 and HP6058) bound to different epitopes in the **CH2 domain** of three of four IgG subclasses. The domain mapping was confirmed by competitive inhibition experiments. These results were used to select a group of IgG-reactive MABs for construction of a poly-monoclonal anti-IgG capture and detection reagent that uniformly bound all four subclasses of human IgG. This study provides support for the use of engineered chimeric human **chimeric antibodies** as replacements for increasingly rare, purified human paraproteins in the specificity analysis of immunochemical reagents used in clinical and research laboratories for the detection and quantitation of human antibodies. Moreover, these studies demonstrate how the MABs can serve as effective probes for examining conformational differences among the four human IgG subclasses.

L2 ANSWER 4 OF 36 MEDLINE on STN

92232133. PubMed ID: 1567557. Mapping rheumatoid factor binding sites using genetically engineered, chimeric IgG antibodies. Bonagura V R; Artandi S E; Agostino N; Tao M H; Morrison S L. (Department of Microbiology, College of Physicians and Surgeons, Columbia University, New York, NY 10032. ) DNA and cell biology, (1992 Apr) 11 (3) 245-52. Journal code: 9004522. ISSN: 1044-5498. Pub. country: United States. Language: English.

AB We are using chimeric IgG antibodies consisting of murine variable regions joined to human constant regions as rheumatoid factor (RF) binding substrates to localize and map IgM RF binding sites on IgG. Using **chimeric antibodies** in a modified RF ELISA, we showed that RFs from rheumatoid arthritis (RA) and Waldenstrom's macroglobulinemia (WMac) patients differ in their binding specificities for IgG3, although some of these RFs share common specificity for IgG1, IgG2, and IgG4. By shuffling constant region domains between IgG3 and IgG4, we showed that sequence variation in the CH3 domain is responsible for WMac-derived RF differentiation of IgG3 and IgG4. By making site-directed mutations in the wild-type IgG3 or IgG4 human gamma constant genes, we showed that His-435 is an essential residue in RF binding to IgG for most WMac RFs. The allotypic polymorphism in IgG3 at 436 is not responsible for differences in previous reports of high-frequency IgG3 binding by WMac RFs. A amino acid loop in the **CH2 domain** of IgG4 proximal to the CH2-CH3 interface is important in WMac RF binding to IgG; a more distal CH2 loop in CH2 has a more variable effect on WMac RF binding. To evaluate the contribution of the N-linked carbohydrate moiety at Asn-297 to RF binding sites on IgG, we measured RF binding to aglycosylated IgG antibodies produced by mutating the glycosylation signal Asn-297 to another amino acid. Of all four IgG subclasses, only aglycosylated IgG3 was a better RF binding substrate than its glycosylated subclass counterpart. (ABSTRACT TRUNCATED AT 250 WORDS)

L2 ANSWER 5 OF 36 MEDLINE on STN

92020986. PubMed ID: 1833770. Identification of the Fc gamma receptor class I binding site in human IgG through the use of recombinant IgG1/IgG2 hybrid and point-mutated antibodies. Chappel M S; Isenman D E; Everett M; Xu Y Y; Dorrington K J; Klein M H. (Department of Immunology, University

of Toronto, ON, Canada. ) Proceedings of the National Academy of Sciences of the United States of America, (1991 Oct 15) 88 (20) 9036-40. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB To characterize the region on human IgG1 responsible for its high-affinity interaction with the human Fc gamma receptor class I (Fc gamma RI), we have analyzed the binding properties of a series of genetically engineered chimeric antinitrophenyl antibodies with identical murine antibody combining sites and hybrid IgG1/IgG2 human constant (C) regions. In addition, we have investigated a panel of reciprocally point-mutated IgG1 and IgG2 **chimeric antibodies** to identify the amino acid residues that confer cytophilic properties to human IgG1. Our data unambiguously indicate that cytophilic activity of IgG1 is an intrinsic property of its heavy-chain C region 2 (**CH2 domain**). We report that the entire sequence spanning residues 234-237 (LLGG) is required to restore full binding activity to IgG2 and IgG4 and that individual amino acid substitutions failed to render IgG2 active. Nevertheless, the reciprocal single point mutations in IgG1 either significantly lowered its activity or abolished it completely. Finally, we observed that an IgG2 antibody containing the entire ELLGGP sequence (residues 233-238) was more active than wild-type IgG1. This finding suggests that in addition to the primary contact site identified in the N terminus of the gamma 1 **CH2 domain**, secondary sites involving residues from the C-terminal half of the domain may also contribute to the IgG1-Fc gamma RI interaction.

L2 ANSWER 6 OF 36 MEDLINE on STN

91178436. PubMed ID: 2007852. The differential ability of human IgG1 and IgG4 to activate complement is determined by the COOH-terminal sequence of the **CH2 domain**. Tao M H; Canfield S M; Morrison S L. (Department of Microbiology, College of Physicians and Surgeons, Columbia University, New York, New York 10032. ) Journal of experimental medicine, (1991 Apr 1) 173 (4) 1025-8. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Using domain switch **chimeric antibodies**, we confirm the important role of CH2 in complement activation. In addition, we demonstrate that the structures responsible for the differential ability of human IgG1 and IgG4 to activate complement are located at the COOH-terminal part (from residue 292 to 340) of the **CH2 domain**. The amino acids in CH2 that might be involved in complement interaction are discussed. While CH3 contributes to efficient complement activation, CH3 from IgG2 and CH3 IgG3 are equally effective.

L2 ANSWER 7 OF 36 MEDLINE on STN

90332649. PubMed ID: 2198570. Serum half-life and tumor localization of a **chimeric antibody** deleted of the **CH2 domain** and directed against the disialoganglioside GD2. Mueller B M; Reisfeld R A; Gillies S D. (Department of Immunology, Research Institute of Scripps Clinic, La Jolla, CA 92037. ) Proceedings of the National Academy of Sciences of the United States of America, (1990 Aug) 87 (15) 5702-5. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Recombinant techniques allow one to engineer an antibody molecule and, in this way, manipulate its properties and functions. We engineered a chimeric human/mouse antibody to the tumor-associated antigen ganglioside GD2, with the aim of decreasing its serum half-life, maintaining its full antigen-binding capacity, and deleting its effector functions, thus making it a potentially useful reagent for the radioimaging of tumors. To this end, the constant region of the human gamma 1 chain was mutated by deleting the second domain (CH2). Here we show that the CH2-deleted antibody (ch14.18-delta CH2) was cleared from the blood of athymic (nu/nu) mice bearing human melanoma tumors with the same kinetics as human IgG F(ab')2. At a beta t1/2 of 12 hr, 0.9% of the injected dose of

125I-labeled ch14.18-delta CH2 was found per milliliter of blood 24 hr after i.v. injection. In biodistribution experiments, 125I-labeled ch14.18-delta CH2 targeted specifically to melanoma xenografts, achieving optimal tumor-to-tissue ratios 12-16 hr after i.v. injection. ch14.18-delta CH2 was localized to the melanoma tumors more rapidly and with better localization ratios than the intact **chimeric antibody** ch14.18. Sixteen hours after i.v. injection, the tumor-to-blood and tumor-to-liver ratios of ch14.18-delta CH2 were 5 and 12, respectively, while optimal localization ratios obtained for ch14.18 were 1 and 5, respectively, but 96 hr after injection. A reagent such as ch14.18-delta CH2 should be useful for radioimmunodetection of human tumors because of reduced immunogenicity, increased targeting specificity, and rapid clearance from circulation.

L2 ANSWER 8 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2004128302 EMBASE The Evaluation of Recombinant, Chimeric, Tetravalent Antihuman CD22 Antibodies. Meng R.; Smallshaw J.E.; Pop L.M.; Yen M.; Liu X.; Le L.; Ghetie M.-A.; Vitetta E.S.; Ghetie V.. E.S. Vitetta, Cancer Immunobiology Center, Univ. of TX Southwestern Med. Ctr., 6000 Harry Hines Boulevard, Dallas, TX 75390-8576, United States. ellen.vitetta@utsouthwestern.edu. Clinical Cancer Research Vol. 10, No. 4, pp. 1274-1281 15 Feb 2004. Refs: 21.

ISSN: 1078-0432. CODEN: CCREF4

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20040415

AB Purpose: The purpose of this study was to prepare chimeric antihuman CD22 tetravalent monoclonal antibodies (MAbs) with high functional affinity, long persistence in the circulation, increased antitumor activity, and conserved effector function in vitro. Experimental Design: We investigated the association/ dissociation rates of these tetravalent antibodies using CD22 (+) Daudi lymphoma cells. We then tested their ability to interact with Fc receptors on a human cell line (U937), to mediate antibody-dependent cellular cytotoxicity with human natural killer cells, to bind human Clq, to inhibit the in vitro growth of CD22 Daudi cells, and to persist in the circulation. Results: The rate of dissociation of the tetravalent MAbs versus the divalent antibody was considerably slower. These tetravalent MAbs inhibited the in vitro proliferation of CD22 Daudi cells at a concentration that was at least 100-fold lower than that of the divalent murine antibody. The tetravalent MAbs containing both the CH2 and CH3 domains and a chimeric recombinant divalent antibody bound similarly to Fc receptor, Clq, and mediate antibody-dependent cellular cytotoxicity equally well with human natural killer cells. The persistence in the circulation of chimeric tetravalent MAbs was considerably longer than that of chemical homodimers. Conclusions: The tetravalent anti-CD22 MAbs with intact Fc regions should make effective therapeutic agents for B-cell tumors.

L2 ANSWER 9 OF 36 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

93120172 EMBASE Document No.: 1993120172. Structural motifs involved in human IgG antibody effector functions. Greenwood J.; Clark M.; Waldmann H.. Dept of Pathology (Immunology Div), Tennis Court Road, Cambridge CB2 1QP, United Kingdom. European Journal of Immunology Vol. 23, No. 5, pp. 1098-1104 1993.

ISSN: 0014-2980. CODEN: EJIMAF

Pub. Country: Germany. Language: English. Summary Language: English.

ED Entered STN: 930530

AB A humanized IgG antibody to CAMPATH-1 antigen (CDw52) is known to be lympholytic both in vitro and in vivo. So as to improve therapeutic potency through protein engineering strategies, we wish to define the structural motifs underlying some of the documented differences in



function between human (h) IgG1 and IgG4 forms of the antibody. By the creation of heavy chain domain-switch and intra-domain recombinant antibodies we have established an important role for the carboxy-terminal half of the **CH2 domain** in determining differential behaviour in antibody-dependent cytotoxicity (ADCC) and in complement lysis. If this same region were necessary for the effector mechanisms that operate in vivo, then it might be possible to improve antibody effector functions by construction of novel antibodies that possess within the one molecule multiple copies of the crucial hinge-CH2 associated structures. Although our previous work suggested that the hIgG4 CAMPATH-1 antibody was ineffective at ADCC, we found this to be so only in some individuals. In others, IgG4, and indeed all the IgG subclasses were able to mediate ADCC. Overall, though, hIgG1 remains the best choice isotype for lytic therapy in vivo.

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92313826 EMBASE Document No.: 1992313826. Mapping rheumatoid factor binding sites using genetically engineered, chimeric IgG antibodies. Bonagura V.R.; Artandi S.E.; Agostino N.; Tao M.-H.; Morrison S.L.. Long Island Jewish Medical Center, Schneider Children's Hospital, 269-01 76th Avenue, New Hyde Park, NY 11042, United States. DNA and Cell Biology Vol. 11, No. 3, pp. 245-252 1992.

ISSN: 1044-5498. CODEN: DCEBE8

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 921108

AB We are using chimeric IgG antibodies consisting of murine variable regions joined to human constant regions as rheumatoid factor (RF) binding substrates to localize and map IgM RF binding sites on IgG. Using **chimeric antibodies** in a modified RF ELISA, we showed that RFs from rheumatoid arthritis (RA) and Waldenstrom's macroglobulinemia (WMac) patients differ in their binding specificities for IgG3, although some of these RFs share common specificity for IgG1, IgG2, and IgG4. By shuffling constant region domains between IgG3 and IgG4, we showed that sequence variation in the C(H)3 domain is responsible for WMac-derived RF differentiation of IgG3 and IgG4. By making site-directed mutations in the wild-type IgG3 or IgG4 human gamma constant genes, we showed that His-435 is an essential residue in RF binding to IgG for most WMac RFs. The allotypic polymorphism in IgG3 at 436 is not responsible for differences in previous reports of high-frequency IgG3 binding by WMac RFs. A amino acid loop in the **CH2 domain** of IgG4 proximal to the CH2-CH3 interface is important in WMac RF binding to IgG; a more distal CH2 loop in CH2 has a more variable effect on WMac RF binding. To evaluate the contribution of the N-linked carbohydrate moiety at Asn-297 to RF binding sites on IgG, we measured RF binding to aglycosylated IgG antibodies produced by mutating the glycosylation signal Asn-297 to another amino acid. Of all four IgG subclasses, only aglycosylated IgG3 was a better RF binding substrate than its glycosylated subclass counterpart. The RF binding site(s) on IgG bound by WMac, some RA derived RFs, and Staphylococcus aureus protein A (SPA) are not identical. Some RFs from RA patients with novel binding specificities for IgG may be disease-specific RFs.

L2 ANSWER 11 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1998:438692 Document No.: PREV199800438692. Chimeric human-mouse IgG antibodies with shuffled constant region exons demonstrate that multiple domains contribute to in vivo half-life. Zuckier, Lionel S. [Reprint author]; Chang, Chee J.; Scharff, Matthew D.; Morrison, Sherie L.. Dep. Nuclear Med., Albert Einstein Coll. Med., Ullmann Build., Room 121, 1300 Morris Park Ave., Bronx, NY 10461, USA. Cancer Research, (Sept. 1, 1998) Vol. 58, No. 17, pp. 3905-3908. print.

CODEN: CNREA8. ISSN: 0008-5472. Language: English.

AB Structural features that determine the differing rates of immunoglobulin catabolism are of great relevance to the engineering of immunologically active reagents. Sequences in the CH2 and CH3 region of IgG have been shown to regulate the rate of clearance through their interaction with FcRn. In an attempt to probe additional structural features that regulate antibody half-life, we have investigated two families of **chimeric antibodies**, composed of identical murine heavy and light antidansyl variable regions joined to human kappa light-chains and wild-type or shuffled human IgG heavy-chain constant regions. These antibodies were iodinated, and their clearance was studied in severe combined immunodeficient mice hosts by whole-body radioactivity measurements. Clearances of the wild-type and recombinant antibodies were biphasic. In a panel of immunoglobulins derived from IgG2 and IgG3, as successive domains were varied from gamma2 to gamma3, beta-phase half-life gradually decreased from 337.0 h to 70.6 h. Statistical analysis suggested that the composition of each of the three domains affected half-life, and no single region of the molecule by itself determined the rate of clearance. In the second panel of immunoglobulins derived from IgG1 and IgG4, the construct with the amino terminus portion of the molecule derived from IgG4, joined within the **CH2 domain** to the COOH terminus portion of IgG1, had a half-life paradoxically greater than either IgG1 or IgG4 ( $P < 0.012$ ). All four IgG1/IgG4 constructs demonstrated presence of the concentration catabolism phenomenon, which is a unique hallmark of immunoglobulin catabolism. The contribution of all three constant region domains to immunoglobulin half-life may be due to distant conformational effects in addition to direct binding to protective receptors, and emphasizes the importance of distant sequences on the rate of immunoglobulin catabolism. Interesting possibilities regarding mechanisms controlling immunoglobulin metabolism are raised by the hybrid gamma4/gamma1 molecule with a half-life greater than either parental immunoglobulin. Understanding the relationships between the structure of these molecules and their clearance rate will further our ability to produce immunoglobulins with improved pharmacokinetic properties.

L2 ANSWER 12 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1993:186789 Document No.: PREV199395097239. Epitope mapping of human immunoglobulin-specific murine monoclonal antibodies with domain-switched, deleted and point-mutated **chimeric antibodies**. Hamilton, Robert G. [Reprint author]; Morrison, Sherie L.. Room 1A20, DACI Laboratory, Johns Hopkins Asthma Allergy Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA. Journal of Immunological Methods, (1993) Vol. 158, No. 1, pp. 107-122. CODEN: JIMMBG. ISSN: 0022-1759. Language: English.

AB 27 engineered **chimeric antibodies** possessing human gamma, epsilon, mu or alpha constant regions and V region specificity for nitrophenyl or dansyl were used to study the isotype specificity of 29 murine monoclonal antibodies (MAbs) specific for human immunoglobulins (IgG1-4, IgE, IgM, IgA or secretory piece). The isotype-restricted immunoreactivity observed with wild-type **chimeric antibodies** paralleled the pattern of each MAb's reactivity with purified human myeloma proteins. 16 mutant IgG anti-dansyl **chimeric antibodies** with genetically engineered domain switches, deletions or point-mutations were used as antigens to further characterize the epitopes recognized by the human IgG subclass-specific MAbs. The binding of three human IgG1-specific MAbs (HP6069, HP6070 and HP6091) was mapped to similar epitopes on the C-H2 domain of human IgG1. Of the two anti-human IgG2 MAbs tested, HP6002 reacted with the C-H2 of IgG2 while HP6014 bound to the C-H1 domain. Both anti-human IgG3 MAbs (HP6047, HP6050) reacted with different region of the IgG3 hinge. The anti-human IgG4 MAbs (HP6023, HP6025) bound to a similar epitope on the carboxyl terminus of C-H2 or the C-H3 of human IgG4. The three exclusion

antibodies (HP6019, HP6030 and HP6058) bound to different epitopes in the C-H2 domain of three of four IgG subclasses. The domain mapping was confirmed by competitive inhibition experiments. These results were used to select a group of IgG-reactive MABs for construction of a poly-monoclonal anti-IgG capture and detection reagent that uniformly bound all four subclasses of human IgG. This study provides support for the use of engineered chimeric human **chimeric antibodies** as replacements for increasingly rare, purified human paraproteins in the specificity analysis of immunochemical reagents used in clinical and research laboratories for the detection and quantitation of human antibodies. Moreover, these studies demonstrate how the MABs can serve as effective probes for examining conformational differences among the four human IgG subclasses.

L2 ANSWER 13 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1992:48909 Document No.: PREV199293028884; BA93:28884. IDENTIFICATION OF THE FC-GAMMA RECEPTOR CLASS I BINDING SITE IN HUMAN IGG THROUGH THE USE OF RECOMBINANT IGG1-IGG2 HYBRID AND POINT-MUTATED ANTIBODIES. CHAPPEL M S [Reprint author]; ISENMAN D E; EVERETT M; XU Y-Y; DORRINGTON K J; KLEIN M H. DEP IMMUNOLOGY, MEDICAL SCIENCES BUILDING, UNIVERSITY TORONTO, TORONTO, ONT, M5S 1A8 CAN. Proceedings of the National Academy of Sciences of the United States of America, (1991) Vol. 88, No. 20, pp. 9036-9040. CODEN: PNASA6. ISSN: 0027-8424. Language: ENGLISH.

AB To characterize the region on human IgG1 responsible for its high-affinity interaction with the human Fcγ receptor class I (FcγRI), we have analyzed the binding properties of a series of genetically engineered chimeric antinitrophenyl antibodies with identical murine antibody combining sites and hybrid IgG1/IgG2 human constant (C) regions. In addition, we have investigated a panel of reciprocally point-mutated IgG1 and IgG12 **chimeric antibodies** to identify the amino acid residues that confer cytophilic properties to human IgG1. Our data unambiguously indicate that cytophilic activity of IgG1 is an intrinsic property of its heavy-chain C region 2 (**CH2 domain**). We report that the entire sequence spanning residues 234-237 (LLGG) is required to restore full binding activity to IgG2 and IgG4 and that individual amino acid substitutions failed to render IgG2 active. Nevertheless, the reciprocal single point mutations in IgG1 either significantly lowered its activity or abolished it completely. Finally, we observed that an IgG2 antibody containing the entire ELLGGP sequence (residues 233-238) was more active than wild-type IgG1. This finding suggests that in addition to the primary contact site identified in the N terminus of the γ1 **CH2 domain**, secondary sites involving residues from the C-terminal half of the domain may also contribute to the IgG1-FcγRI interaction.

L2 ANSWER 14 OF 36 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1991:249831 Document No.: PREV199191130386; BA91:130386. THE DIFFERENTIAL ABILITY OF HUMAN IGG1 AND IGG4 TO ACTIVATE COMPLEMENT IS DETERMINED BY THE CARBOXYL-TERMINAL SEQUENCE OF THE C-H2 DOMAIN. TAO M-H [Reprint author]; CANFIELD S M; MORRISON S L. DEP MICROBIOL MOL BIOL INST, UNIV CALIF LOS ANGELES, LOS ANGELES, CALIF 90024, USA. Journal of Experimental Medicine, (1991) Vol. 173, No. 4, pp. 1025-1028. CODEN: JEMEAU. ISSN: 0022-1007. Language: ENGLISH.

AB Using domain switch **chimeric antibodies**, we confirm the important role of CH2 in complement activation. In addition, we demonstrate that the structures responsible for the differential ability of human IgG1 and IgG4 to activate complement are located at the COOH-terminal part (from residue 292 to 340) of the **CH2 domain**. The amino acid in CH2 that might be involved in complement interaction are discussed. While CH3 contributes to efficient complement activation, CH3 from IgG2 and CH3 IgG3 are equally effective.

L2 ANSWER 15 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1998:778085 The Genuine Article (R) Number: 127GV. Therapy with monoclonal antibodies. II. The contribution of Fc gamma receptor binding and the influence of C(H)1 and C(H)3 domains on in vivo effector function. Isaacs J D (Reprint); Greenwood J; Waldmann H. St James Univ Hosp, Mol Med Unit, Clin Sci Bldg, Leeds LS9 7TF, W Yorkshire, England (Reprint); Univ Cambridge, Dept Pathol, Div Immunol, Cambridge CB2 1QP, England. JOURNAL OF IMMUNOLOGY (15 OCT 1998) Vol. 161, No. 8, pp. 3862-3869. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB An in vivo model is used to define Fe motifs engaged by mAbs to deplete target cells. Human IgG1 and human IgG4 were very potent, and mutations within a motif critical for Fc gamma R binding (glutamate 233 to proline, leucine/phenylalanine 234 to valine, and leucine 235 to alanine) completely prevented depletion, Mouse IgG2b was also potent, and mutations to prevent complement activation did not impair depletion with this isotype, as previously shown for human IgG1. In contrast, a mutation that impaired binding to mouse Fc gamma RII (glutamate 318 to alanine) eliminated effector function of mouse IgG2b and also reduced the potency of human IgG4. To reveal potential contributions of domains other than C(H)2, domain switch mutants were created between human IgG1 and rat IgG2a, Two hybrid mAbs were generated with potencies exceeding anything previously seen in this model, While their mechanism of depletion was not defined, their activity appeared dependent upon interdomain interactions in the Pc region.

L2 ANSWER 16 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1998:660658 The Genuine Article (R) Number: 115FE. Chimeric human-mouse IgG antibodies with shuffled constant region exons demonstrate that multiple domains contribute to in vivo half-life. Zuckier L S (Reprint); Chang C J; Scharff M D; Morrison S L. Yeshiva Univ Albert Einstein Coll Med, Dept Nucl Med, 1300 Morris Pk Ave, Ullmann Bldg, Room 121, Bronx, NY 10461 USA (Reprint); Yeshiva Univ Albert Einstein Coll Med, Dept Nucl Med, Bronx, NY 10461 USA; Yeshiva Univ Albert Einstein Coll Med, Dept Epidemiol & Biostat, Bronx, NY 10461 USA; Yeshiva Univ Albert Einstein Coll Med, Dept Cell Biol, Bronx, NY 10461 USA; Univ Calif Los Angeles, Dept Microbiol & Mol Genet, Los Angeles, CA 90095 USA; Univ Calif Los Angeles, Inst Mol Biol, Los Angeles, CA 90095 USA. CANCER RESEARCH (1 SEP 1998) Vol. 58, No. 17, pp. 3905-3908. ISSN: 0008-5472. Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202 USA. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Structural features that determine the differing rates of immunoglobulin catabolism are of great relevance to the engineering of immunologically active reagents. Sequences in the C(H)2 and C(H)3 region of IgG have been shown to regulate the rate of clearance through their interaction with FcRn. In an attempt to probe additional structural features that regulate antibody half-life, we have investigated two families of **chimeric antibodies**, composed of identical murine heavy and light antidiary variable regions joined to human kappa light-chains and wild-type or shuffled human IgG heavy-chain constant regions. These antibodies were iodinated, and their clearance was studied in severe combined immunodeficient mice hosts by whole-body radioactivity measurements. Clearances of the wildtype and recombinant antibodies were biphasic. In a panel of immunoglobulins derived from IgG, and IgG, as successive domains were varied from gamma(2) to gamma(3), beta-phase half-life gradually decreased from 337.0 h to 70.6 h. Statistical analysis suggested that the composition of each of the three domains affected half-life, and no single region of the molecule by itself determined the rate of clearance. In the second panel of immunoglobulins

derived from IgG(1) and IgG(4), the construct with the amino terminus portion of the molecule derived from IgG(4), joined within the C(H)2 domain to the COOH terminus portion of IgG,, had a half-life paradoxically greater than either IgG(1) or IgG(4) (P < 0.012). All four IgG(1)/IgG(4) constructs demonstrated presence of the concentration catabolism phenomenon, which is a unique hallmark of immunoglobulin catabolism. The contribution of all three constant region domains to immunoglobulin half-life may be due to distant conformational effects in addition to direct binding to protective receptors, and emphasizes the importance of distant sequences on the rate of immunoglobulin catabolism. Interesting possibilities regarding mechanisms controlling immunoglobulin metabolism are raised by the hybrid gamma(4)/gamma(1), molecule with a half-life greater than either parental immunoglobulin. Understanding the relationships between the structure of these molecules and their clearance rate will further our ability to produce immunoglobulins with improved pharmacokinetic properties.

L2 ANSWER 17 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1995:126358 The Genuine Article (R) Number: QH291. ADDITION OF A MU-TAILPIECE TO IGG RESULTS IN POLYMERIC ANTIBODIES WITH ENHANCED EFFECTOR FUNCTIONS INCLUDING COMPLEMENT-MEDIATED CYTOLYSIS BY IGG4. SMITH R I F (Reprint); COLOMA M J; MORRISON S L. UNIV CALIF LOS ANGELES, DEPT MICROBIOL & MOLEC GENET, LOS ANGELES, CA 90024; UNIV CALIF LOS ANGELES, INST MOLEC BIOL, LOS ANGELES, CA 90024. JOURNAL OF IMMUNOLOGY (1 MAR 1995) Vol. 154, No. 5, pp. 2226-2236. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The 18-amino acid carboxyl-terminal tailpiece from IgM (mu tp) has now been added to the carboxyl-termini of IgG1, IgG2, IgG3, and IgG4 constant regions to produce recombinant IgM-like IgGs. Polymeric IgCs obtained by this approach possess up to six Fcs and 12 antigen-combining sites, greatly increasing the avidity of their interactions with other molecules. Not surprisingly, the C activity of normally active IgG1 and IgG3 and somewhat less active IgG2 Abs is shown to be dramatically enhanced upon polymerization. The multiple Fcs present in a single molecule apparently allow for more efficient interactions with the multiple Clq heads present in C1, the first component of the classical C cascade. An unexpected result however, is that IgG4, normally devoid of C activity, when polymerized in the same fashion directs C-mediated lysis of target cells almost as effectively as the other polymers. Interestingly though, IgG4 mu tp does not deplete C activity in a standard consumption assay using soluble Ag. The other gamma mu tp isotypes are capable of depleting 100% of the serum lytic ability even in the absence of Ag, whereas IgG4 mu tp shows no evidence of activity in this assay under any of the conditions tested. Additionally, we show that, in contrast to monomeric IgG, polymeric IgCs bind with very high affinity to Fc gamma receptor II (Fc gamma RII), a low affinity receptor for wild-type antibodies; however, binding to Fc gamma RI, the high affinity receptor, appears to be unaltered. Finally, the in vivo t(1/2) of the gamma mu tp proteins is decreased relative to wild-type IgG, apparently because of rapid clearance of the polymeric fraction.

L2 ANSWER 18 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1995:111533 The Genuine Article (R) Number: QG208. INTERACTION OF HUMAN MONOCYTE FC-GAMMA RECEPTORS WITH RAT IGG2B - A NEW INDICATOR FOR THE FC-GAMMA-RIIA (R-H131) POLYMORPHISM. HAAGEN I A (Reprint); GEERARS A J G; CLARK M R; VANDEWINKEL J G J. UNIV UTRECHT HOSP, DEPT IMMUNOL F03821, POSTBOX 85500, 3508 GA UTRECHT, NETHERLANDS (Reprint); UNIV CAMBRIDGE, DEPT PATHOL, CAMBRIDGE, ENGLAND. JOURNAL OF IMMUNOLOGY (15 FEB 1995) Vol. 154, No. 4, pp. 1852-1860. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Rat mAbs receive considerable interest for immunologic intervention in man. The rat IgG2b isotype has previously been found to be optimally active both in vivo and in vitro. We found that both a rat IgG2b CD3 mAb and a monovalent hybrid rat IgG2b-mouse IgG1 bispecific Ab triggered T cell activation in PBMC. Inhibition analyses with mAb blocking different human IgG Fc receptors (Fc gamma R) showed a dimorphic pattern. In donors expressing an Fc gamma RIIa-R/R131 allotype (previously defined on the basis of interaction with mouse (m) IgG1 as 'high responder') anti-Fc gamma RI mAb 197 inhibited rat IgG2b induced T cell mitogenesis almost completely. In Fc gamma RIIa-H/H131 ('low responder' allotype) donors, however, both anti-Fc gamma RI mAb 197 and anti-Fc gamma RII mAb IV.3 were essential for optimal inhibition of mitogenesis. T cell proliferation experiments performed with the use of Fc gamma R-transfected fibroblasts as accessory cells showed the high affinity Fc gamma RIa (CD64) to interact with both rat IgG2b and rat IgG2b-mlgG1 hybrid CD3 mAb. The use of the two types of Fc gamma RIIa (CD32)-transfectants instead showed rat IgG2b CD3 mAb to interact solely with the IIA-H/H131 allotype. Interestingly, rat IgG2b-mlgG1 hybrid mAb did not interact effectively with this low affinity Fc gamma R. This suggests a requirement for only one rat IgG2b H chain for Fc gamma RIa-mediated binding, whereas two identical H chains seem to be necessary for proper interaction with Fc gamma RIIa. Ab-sensitized RBC-rosette experiments performed with the use of a rat IgG2b anti-NIP mAb confirmed the interaction pattern observed with rat CD3 mAb, supporting the phenomena to be isotype-, and not mAb-, dependent. These analyses point to a unique reactivity pattern for rat IgG2b Abs, interacting both with the high affinity Fc gamma RIa in all donors and Fc gamma RIIa of individuals expressing the IIA-H131 allotype.

L2 ANSWER 19 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1993:474217 The Genuine Article (R) Number: LP830. STRUCTURAL FEATURES OF HUMAN IMMUNOGLOBULIN-G THAT DETERMINE ISOTYPE-SPECIFIC DIFFERENCES IN COMPLEMENT ACTIVATION. TAO M H (Reprint); SMITH R I F; MORRISON S L. UNIV CALIF LOS ANGELES, INST MOLEC BIOL, LOS ANGELES, CA 90024; UNIV CALIF LOS ANGELES, DEPT MICROBIOL & MOLEC GENET, LOS ANGELES, CA 90024. JOURNAL OF EXPERIMENTAL MEDICINE (1 AUG 1993) Vol. 178, No. 2, pp. 661-667. ISSN: 0022-1007. Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Although very similar in sequence, the four subclasses of human immunoglobulin G (IgG) differ markedly in their ability to activate complement. Glu318-Lys320-Lys322 has been identified as a key binding motif for the first component of complement, Clq, and is present in all isotypes of Ig capable of activating complement. This motif, however, is present in all subclasses of human IgG, including those that show little (IgG2) or even no (IgG4) complement activity. Using point mutants of **chimeric antibodies**, we have identified specific residues responsible for the differing ability of the IgG subclasses to fix complement. In particular, we show that Ser at position 331 in gamma4 is critical for determining the inability of that isotype to bind Clq and activate complement. Additionally, we provide further evidence that levels of Clq binding do not necessarily correlate with levels of complement activity, and that Clq binding alone is not sufficient for complement activation.

L2 ANSWER 20 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1992:474909 The Genuine Article (R) Number: JG734. MAPPING RHEUMATOID-FACTOR BINDING-SITES USING GENETICALLY ENGINEERED, CHIMERIC IGG ANTIBODIES. BONAGURA V R (Reprint); ARTANDI S E; AGOSTINO N; TAO M H; MORRISON S L. LONG ISL JEWISH MED CTR, SCHNEIDER CHILDRENS HOSP, DEPT PEDIAT, NEW HYDE PK, NY 11042 (Reprint); YESHIVA UNIV ALBERT EINSTEIN COLL MED, BRONX, NY

10461; COLUMBIA UNIV COLL PHYS & SURG, DEPT MICROBIOL, NEW YORK, NY 10032; UNIV CALIF LOS ANGELES, INST MOLEC BIOL, DEPT MICROBIOL, LOS ANGELES, CA 90024. DNA AND CELL BIOLOGY (APR 1992) Vol. 11, No. 3, pp. 245-252. ISSN: 1044-5498. Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB

We are using chimeric IgG antibodies consisting of murine variable regions joined to human constant regions as rheumatoid factor (RF) binding substrates to localize and map IgM RF binding sites on IgG. Using **chimeric antibodies** in a modified RF ELISA, we showed that RFs from rheumatoid arthritis (RA) and Waldenstrom's macroglobulinemia (WMac) patients differ in their binding specificities for IgG3, although some of these RFs share common specificity for IgG1, IgG2, and IgG4. By shuffling constant region domains between IgG3 and IgG4, we showed that sequence variation in the CH3 domain is responsible for WMac-derived RF differentiation of IgG3 and IgG4. By Making site-directed mutations in the wild-type IgG3 or IgG4 human gamma constant genes, we showed that His-435 is an essential residue in RF binding to IgG for most WMac RFs. The allotypic polymorphism in IgG3 at 436 is not responsible for differences in previous reports of high-frequency IgG3 binding by WMac RFs. A amino acid loop in the **CH2 domain** of IgG4 proximal to the CH2-CH3 interface is important in WMac RF binding to IgG; a more distal CH2 loop in CH2 has a more variable effect on WMac RF binding. To evaluate the contribution of the N-linked carbohydrate moiety at Asn-297 to RF binding sites on IgG, we measured RF binding to aglycosylated IgG antibodies produced by mutating the glycosylation signal Asn-297 to another amino acid. Of all four IgG subclasses, only aglycosylated IgG3 was a better RF binding substrate than its glycosylated subclass counterpart. The RF binding site(s) on IgG bound by WMac, some RA derived RFs, and Staphylococcus aureus protein A (SPA) are not identical. Some RFs from RA patients with novel binding specificities for IgG may be disease-specific RFs.

L2 ANSWER 21 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1992:145548 The Genuine Article (R) Number: HG033. MULTIPLE BINDING-SITES ON THE **CH2 DOMAIN** OF IGG FOR MOUSE FC-GAMMA-R11. LUND J (Reprint); POUND J D; JONES P T; DUNCAN A R; BENTLEY T; GOODALL M; LEVINE B A; JEFFERIS R; WINTER G. UNIV CAMBRIDGE, SCH MED, MRC, MOLEC BIOL LAB, HILLS RD, CAMBRIDGE CB2 2QH, ENGLAND; UNIV BIRMINGHAM, SCH MED, DEPT IMMUNOL, BIRMINGHAM B15 2TJ, W MIDLANDS, ENGLAND; UNIV BIRMINGHAM, DEPT BIOCHEM, BIRMINGHAM B15 2TJ, W MIDLANDS, ENGLAND. MOLECULAR IMMUNOLOGY (JAN 1992) Vol. 29, No. 1, pp. 53-59. ISSN: 0161-5890. Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB

Important mammalian defensive functions such as phagocytosis are triggered in leukocytes by the interaction of the Fc region of IgG with cell surface receptors (Fc-gamma-R). The C(H) 2 domain of IgG has been implicated previously as the site of interaction with human and mouse Fc-gamma-R. This domain was mapped for interaction with mouse Fc-gamma-R11 expressed by the macrophage-like cell line P388D1, using two panels of a total of 32 site-directed mutants of mouse IgG2b and chimeric human IgG3 monoclonal antibodies. Two potential binding sites have been identified: one in or within the vicinity of the lower hinge site on IgG for human Fc-gamma-R1, and one within the binding site on IgG for Clq. The three mutant IgGs (Gly 237 --> Ala, Asn 297 --> Ala, and Glu 318 --> Ala) which do not interact in complexed form also fail to bind as monomers. A H-1 NMR study of the three non-binding monomeric mutants suggests that the mutations are largely site-specific, indicating that IgG interacts with mouse Fc-gamma-R 11 at two regions within the C(H) 2 domain. This interaction dictates phagocytosis mediated by Fc-gamma-R 11 of the P388D1 cell line.

L2 ANSWER 22 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1991:186060 The Genuine Article (R) Number: FE128. THE DIFFERENTIAL ABILITY OF HUMAN IGG1 AND IGG4 TO ACTIVATE COMPLEMENT IS DETERMINED BY THE COOH-TERMINAL SEQUENCE OF THE **CH2 DOMAIN**. TAO M H (Reprint); CANFIELD S M; MORRISON S L. UNIV CALIF LOS ANGELES, DEPT MICROBIOL & MOLEC GENET, LOS ANGELES, CA 90024; COLUMBIA UNIV COLL PHYS & SURG, DEPT MICROBIOL, NEW YORK, NY 10032. JOURNAL OF EXPERIMENTAL MEDICINE (1 APR 1991) Vol. 173, No. 4, pp. 1025-1028. ISSN: 0022-1007. Publisher: ROCKEFELLER UNIV PRESS, 222 E 70TH STREET, NEW YORK, NY 10021. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Using domain switch **chimeric antibodies**, we confirm the important role of C(H)2 in complement activation. In addition, we demonstrate that the structures responsible for the differential ability of human IgG1 and IgG4 to activate complement are located at the COOH-terminal part (from residue 292 to 340) of the C(H)2 domain. The amino acids in C(H)2 that might be involved in complement interaction are discussed. While C(H)3 contributes to efficient complement activation, C(H)3 from IgG2 and C(H)3 IgG3 are equally effective.

L2 ANSWER 23 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1991:66105 The Genuine Article (R) Number: EU557. MOLECULAR DEFINITION OF INTERACTION SITES ON HUMAN-IGG FOR FC-RECEPTORS (HUF-C-GAMMA-R). JEFFERIS R (Reprint); LUND J; POUND J. UNIV BIRMINGHAM, SCH MED, DEPT IMMUNOL, BIRMINGHAM B15 2TJ, W MIDLANDS, ENGLAND (Reprint). MOLECULAR IMMUNOLOGY (DEC 1990) Vol. 27, No. 12, pp. 1237-1240. ISSN: 0161-5890. Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Evidence from several experimental approaches allows us to conclude that the primary amino acid sequence of the lower hinge region (residues 234-237) of human IgG molecules determines recognition by human Fc-gamma RII and Fc-gamma RIII. Glycosylation of the **CH2 domain** is also essential, although the carbohydrate is not accessible for direct interaction with ligands. The role of the carbohydrate moiety may be to maintain a protein conformation that allows accessibility to amino acid side chains essential for ligand recognition and binding. It appears logical that the evolutionarily-related Fc-gamma R molecules should interact with overlapping non-identical sites on the IgG molecule.

L2 ANSWER 24 OF 36 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1990:424319 The Genuine Article (R) Number: DR714. SERUM HALF-LIFE AND TUMOR-LOCALIZATION OF A **CHIMERIC ANTIBODY** DELETED OF THE **CH2 DOMAIN** AND DIRECTED AGAINST THE DISIALOGLANGLIOSIDE-GD2. MUELLER B M (Reprint); REISFELD R A; GILLIES S D. SCRIPPS CLIN & RES FDN, RES INST, DEPT IMMUNOL, 10666 N TORREY PINES RD, LA JOLLA, CA 92037 (Reprint); ABBOTT BIOTECH INC, NEEDHAM HTS, MA 02194. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA (AUG 1990) Vol. 87, No. 15, pp. 5702-5705. ISSN: 0027-8424. Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418. Language: English.

L2 ANSWER 25 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

2005:547519 Document No. 143:76825 Antibodies specific to intracellular cancer-associated antigen for diagnosis, prognosis and apoptosis-inducing therapy of smaller tumors and micrometastases. Evans, Elizabeth E.; Paris, Mark J.; Sahasrabudhe, Deepak M.; Smith, Ernest S.; Zauderer, Maurice (Vaccinex, Inc., USA). PCT Int. Appl. WO 2005055936 A2 20050623,



255 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US40573 20041206. PRIORITY: US 2003-2003/PV52657U 20031204; US 2003-2003/PV531688 20031223.

AB The invention provides in vitro and in vivo methods of killing cancer cells, including therapeutic methods in humans, and also provides antibodies specific for the cancer-specific antigen C35, and polynucleotides encoding such antibodies, as well as therapeutic and diagnostic methods of using such antibodies. The antibodies may also target other internal cancer-associated antigen or prenylated proteins such as CENP-F kinetochore protein, CAAX box protein 1, DnaJ homolog subfamily A member 1, DnaJ homolog subfamily A member 2, guanine nucleotide-binding protein G(I)/G(S)/G(O)  $\gamma$ -5 subunit, nucleotide-binding protein G(I)/G(S)/G(O)  $\gamma$ -10 subunit, nucleotide-binding protein G(I)/G(S)/G(O)  $\gamma$ -12 subunit, lamin B1, lamin B2, lamin A/C, protein phosphatase 1 regulatory inhibitor subunit 16A, peroxisomal farnesylated protein, etc. The antibodies are human, chimeric or humanized antibodies or Fab, F(ab')<sub>2</sub> and scFv fragments, and antibody conjugates or complexes with toxin or radioisotope.

L2 ANSWER 26 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

2004:802261 Document No. 141:312947 Immunoglobulin **CH2**

**domain**-containing Fc or N-linked glycans, galactosylated glycoproteins or antibodies for treating inflammation, cancer, neurofibromatosis, neuropathy and cardiac hypertrophy. Raju, T. Shantha (Genentech, Inc., USA). U.S. Pat. Appl. Publ. US 2004191256 A1 20040930, 27 pp., Cont.-in-part of U.S. Ser. No. 102,865, abandoned. (English). CODEN: USXXCO. APPLICATION: US 2003-719603 20031121. PRIORITY: US 1997-PV50633 19970624; US 1998-102865 19980623.

AB This invention relates to novel glycoprotein glycoform preps. comprising the substantially homogeneous glycoprotein glycoforms. More particularly the invention relates to substantially homogeneous glycoprotein preps. comprising a particular Fc glycan and methods for producing, detecting, enriching and purifying the glycoforms. The invention further relates to Igs and especially antibodies comprising a **CH2 domain** having a particular glycan. Provided are compns. including pharmaceutical compns. and methods of using the preps. as well as articles of manufacture comprising the preps. The antibody is a monoclonal antibody, IgG, IgG1, or immunoadhesin, such as monoclonal anti-CD20, anti-HER2, anti-IgE, anti-VEGF antibody, TNF-IgG1 chimera, or antibody-immunoadhesin chimera. These monoclonal antibodies or **chimeric antibodies** are useful for treating inflammation, cancer, neurofibromatosis, peripheral neuropathologies and cardiac hypertrophy.

L2 ANSWER 27 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

2001:208294 Document No. 134:247945 Transgenic animal milk for the production of recombinant antibody fusion proteins for therapeutic, diagnostic and industry use. Edge, Michael D.; Pollock, Dan; Echelard, Yann; Meade, Harry M.; Rybak, Susanna M. (Genzyme Transgenics Corp., USA; AstraZeneca AB; United States Dept. of Health and Human Services). PCT Int. Appl. WO 2001019846 A1 20010322, 74 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA,

GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English).  
CODEN: PIXXD2. APPLICATION: WO 2000-US25560 20000918. PRIORITY: US  
1999-398610 19990917.

AB A method of making transgenic animals that selectively express genes for recombinant antibody fusion in mammary epithelial cells for therapeutic agent production is described. The method includes providing a transgenic animal expressing a transgene for the fusion protein; allowing the transgene to be expressed; and recovering the fusion protein from the milk of the transgenic animal. The invention is exemplified by preparation of antibody-Carboxypeptidase B fusion protein, anti-transferrin receptor antibody/angiogenin fusion protein, antihuman transferrin receptor antibody and antibody-angiogenin fusion protein. DNA vectors expressing the entire heavy chain of monoclonal E6 (a **chimeric antibody** against the human transferrin receptor), or an antibody-enzyme fusion protein of human RNase and angiogenin () and the **CH2 domain** of the antibody are constructed for the specific expression in the mammary gland in transgenic mice and goat. Biol. characterization of these antibody-angiogenin fusion products are presented.

L2 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

1999:691228 Document No. 131:321542 Chimeric immunoglobulins contg. CH domains of IgA. Morrison, Sherie L.; Chintalacharuvu, Koteswara R.; Yoo, Esther Mikyung; Trinh, Kham M.; Coloma, M. Josefina (The Regents of the University of California, USA). PCT Int. Appl. WO 9954484 A1 19991028, 67 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US8647 19990420. PRIORITY: US 1998-82578 19980420; US 1998-96085 19980811.

AB The authors disclose the preparation of modified Ig mols. using exon exchange. In one example, the modified antibody in IgG2 and contains a CH3 domain of an IgA mol. ( $\alpha$  CH3). The combination of an  $\alpha$  CH3 with other domains selected from one or more non-IgA antibodies provides for an Ig mol. that has the capacity to bind J chain and/or secretory component together with features of a non-IgA antibody. The modified Igs can also contain a CH1 and/or a **CH2 domain** of an IgA mol. The combination of an  $\alpha$  CH1 and/or a **CH2 domain** with other domains selected from one or more non-IgA antibodies provides for the capacity to form higher polymers (trimers, tetramers, pentamers, etc.). The **chimeric antibodies** can also be engineered to lack one or more carbohydrate addition sites.

L2 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

1998:588899 Document No. 129:301448 Chimeric human-mouse IgG antibodies with shuffled constant region exons demonstrate that multiple domains contribute to in vivo half-life. Zuckier, Lionel S.; Chang, Chee J.; Scharff, Matthew D.; Morrison, Sherie L. (Department of Nuclear Medicine, Albert Einstein College of Medicine, Bronx, NY, 10461, USA). Cancer Research, 58(17), 3905-3908 (English) 1998. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB Structural features that determine the differing rates of Ig catabolism are of great relevance to the engineering of immunol. active reagents. Sequences in the CH2 and CH3 region of IgG have been shown to regulate the rate of clearance through their interaction with FcRn. To probe addnl. structural features that regulate antibody half-life, the authors have investigated two families of **chimeric antibodies**, composed of identical murine heavy and light anti-dansyl variable regions joined to human  $\kappa$  light-chains and wild-type or shuffled human IgG heavy-chain

constant regions. These antibodies were iodinated, and their clearance was studied in severe combined immunodeficient mice hosts by whole-body radioactivity measurements. Clearances of the wild-type and recombinant antibodies were biphasic. In a panel of Igs derived from IgG2 and IgG3, as successive domains were varied from  $\gamma 2$  to  $\gamma 3$ ,  $\beta$ -phase half-life gradually decreased from 337.0 h to 70.6 h. Statistical anal. suggested that the composition of each of the three domains affected half-life, and no single region of the mol. by itself determined the rate of clearance. In the second panel of Igs derived from IgG1 and IgG4, the construct with the amino terminus portion of the mol. derived from IgG4, joined within the **CH2 domain** to the COOH terminus portion of IgG1, had a half-life paradoxically greater than either IgG1 or IgG4. All four IgG1/IgG4 constructs demonstrated presence of the concentration catabolism phenomenon, which is a unique hallmark of Ig catabolism. The contribution of all three constant region domains to Ig half-life may be due to distant conformational effects in addition to direct binding to protective receptors, and emphasizes the importance of distant sequences on the rate of Ig catabolism. Interesting possibilities regarding mechanisms controlling Ig metabolism are raised by the hybrid  $\gamma 4/\gamma 1$  mol. with a half-life greater than either parental Ig. Understanding the relationships between the structure of these mols. and their clearance rate will further the authors' ability to produce Igs with improved pharmacokinetic properties.

L2 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

1994:262446 Document No. 120:262446 Construction and purification of domain-deleted immunoglobulin variants of the recombinant/chimeric B72.3 ( $\gamma 1$ ) monoclonal antibody. Calvo, Benjamin; Kashmiri, S.V.S.; Hutzell, Paula; Hand, Patricia Horan; Slavin-Chiorini, Dale C.; Schlom, Jeffrey; Zaremba, Sam (Lab. Tumor Immunol. Biol., Natl. Cancer Inst., Bethesda, MD, 20892, USA). Cancer Biotherapy, 8(1), 95-109 (English) 1993. CODEN: CNBTB. ISSN: 1062-8401.

AB **Chimeric antibodies** have been produced against a pancarcinomic tumor associated antigen, TAG-72, by fusing the genes for the variable region of mouse MAb B72.3 to the genes for the constant region of human IgG. In the authors' efforts to optimize the pharmacokinetics of plasma clearance and the efficiency of tumor localization and penetrance of cB72.3, the authors have now developed truncated versions of Ig heavy chains. The domain-deleted antibodies are produced by transfecting cells that produce chimeric kappa chains with expression vectors that encode chimeric heavy chains lacking the sequences that encode the **CH2 domain**, **CH3 domain**, or both. Despite the absence of these domains, the transfectomas secrete H2L2 tetramers with appropriate antigenic specificity. All the domain-deleted Igs can be purified by chromatog. on Protein G Sepharose which binds to a site on the Fab region that is retained in the domain-deleted antibodies. The CH2CH3 domain-deleted Ig produced in cell culture is analogous in size to enzymically produced F(ab')<sub>2</sub>.

L2 ANSWER 31 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

1993:166980 Document No. 118:166980 Epitope mapping of human immunoglobulin-specific murine monoclonal antibodies with domain-switched, deleted and point-mutated **chimeric antibodies**. Hamilton, Robert G.; Morrison, Sherie L. (Div. Clin. Immunol., Dep. Med., Johns Hopkins Univ. Sch. Med., Baltimore, MD, 21224, USA). Journal of Immunological Methods, 158(1), 107-22 (English) 1993. CODEN: JIMMBG. ISSN: 0022-1759.

AB Some 27 engineered **chimeric antibodies** possessing human  $\gamma$ ,  $\epsilon$ ,  $\mu$ , or  $\alpha$  constant regions and V region specificity for nitrophenyl or dansyl were used to study the isotype specificity of 29 murine monoclonal antibodies (MAbs) specific for human Igs (IgG1-4, IgE, IgM, IgA, or secretory piece). The isotype-restricted immunoreactivity observed with wild-type **chimeric antibodies** paralleled the pattern of each MAb's reactivity with

purified human myeloma proteins. Sixteen mutant IgG anti-dansyl **chimeric antibodies** with genetically engineered domain switches, deletions, or point mutations were used as antigens to further characterize the epitopes recognized by the human IgG subclass-specific MABs. The binding of three human IgG1-specific MABs (HP6069, HP6070, and HP6091) was mapped to similar epitopes on the **CH2 domain** of human IgG1. Of the two anti-human IgG2 MABs tested, HP6002 reacted with the CH2 of IgG2 while HP6014 bound to the CH1 domain. Both anti-human IgG3 MABs (HP6047, HP6050) reacted with different regions of the IgG3 hinge. The anti-human IgG4 MABs (HP6023, HP6025) bound to a similar epitope on the C-terminus of CH2 or the CH3 of human IgG4. The three exclusion antibodies (HP6019, HP6030, and HP6058) bound to different epitopes in the **CH2 domain** of three of four IgG subclasses. The domain mapping was confirmed by competitive inhibition expts. These results were used to select a group of IgG-reactive MABs for construction of a poly-monoclonal anti-IgG capture and detection reagent that uniformly bound all four subclasses of human IgG. This study provides support for the use of engineered chimeric human **chimeric antibodies** as replacements for increasingly rare, purified human paraproteins in the specificity anal. of immunochem. reagents used in clin. and research labs. for the detection and quantitation of human antibodies. Moreover, these studies demonstrate how the MABs can serve as effective probes for examining conformational differences among the four human IgG subclasses.

L2 ANSWER 32 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

1992:253641 Document No. 116:253641 Mapping rheumatoid factor binding sites using genetically engineered, chimeric IgG antibodies. Bonagura, Vincent R.; Artandi, Steven E.; Agostino, Nicodemo; Tao, Mi Hua; Morrison, Sherie L. (Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA). DNA and Cell Biology, 11(3), 245-52 (English) 1992. CODEN: DCEBE8. ISSN: 1044-5498.

AB Chimeric IgG antibodies consisting of murine variable regions joined to human constant regions were used as rheumatoid factor (RF) binding substrates to localize and map IgM RF binding sites on IgG. Using **chimeric antibodies** in a modified RF ELISA, it was shown that RFs from rheumatoid arthritis (RA) and Waldenstrom's macroglobulinemia (WMac) patients differ in their binding specificities for IgG3, although some of these RFs share common specificity for IgG1, IgG2, and IgG4. By shuffling constant region domains between IgG3 and IgG4, it was shown that sequence variation in the CH3 domain is responsible for WMac-derived RF differentiation of IgG3 and IgG4. By making site-directed mutations in the wild-type IgG3 or IgG4 human  $\gamma$  constant genes, it was shown that His-435 is an essential residue in RF binding to IgG for most WMac RFs. The allotypic polymorphism in IgG3 at 436 is not responsible for differences in previous reports of high-frequency IgG3 binding by WMac RFs. An amino acid loop in the **CH2 domain** of IgG4 proximal to the CH2-CH3 interface is important in WMac RF binding to IgG; a more distal CH2 loop in CH2 has a more variable effect on WMac RF binding. To evaluate the contribution of the N-linked carbohydrate moiety at Asn-297 to RF binding sites on IgG, RF binding was measured to aglycosylated IgG antibodies produced by mutating the glycosylation signal Asn-297 to another amino acid. Of all 4 IgG subclasses, only aglycosylated IgG3 was a better RF binding substrate than its glycosylated subclass counterpart. The RF binding site(s) on IgG bound by WMac, some RA derived RFs, and Staphylococcus aureus protein A (SPA) are not identical. Some RFs from RA patients with novel binding specificities for IgG may be disease-specific RFs.

L2 ANSWER 33 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

1991:677551 Document No. 115:277551 Identification of the Fc $\gamma$  receptor class I binding site in human IgG through the use of recombinant IgG1/IgG2 hybrid and point-mutated antibodies. Chappel, M. Suzanne; Isenman, David

- E.; Everett, Margaret; Xu, Yuan Yuan; Dorrington, Keith J.; Klein, Michael H. (Dep. Immunol., Univ. Toronto, Toronto, ON, M5S 1A8, Can.).  
 Proceedings of the National Academy of Sciences of the United States of America, 88(20), 9036-40 (English) 1991. CODEN: PNASA6. ISSN: 0027-8424.
- AB To characterize the region on human IgG1 responsible for its high-affinity interaction with the human Fc $\gamma$  receptor class I (Fc $\gamma$ RI), the authors have analyzed the binding properties of a series of genetically engineered chimeric antidinitrophenyl antibodies with identical murine antibody combining sites and hybrid IgG1/IgG2 human constant (C) regions. In addition, a panel of reciprocally point-mutated IgG1 and IgG2 **chimeric antibodies** was investigated to identify the amino acid residues that confer cytophilic properties to human IgG1. The data unambiguously indicate that cytophilic activity of IgG1 is an intrinsic property of its heavy-chain C region 2 (**CH2**) **domain**. The entire sequence spanning residues 234-237 (LLGG) is required to restore full binding activity to IgG2 and IgG4 and individual amino acid substitutions failed to render IgG2 active. Nevertheless, the reciprocal single point mutations in IgG1 either lowered its activity or abolished it completely. An IgG2 antibody containing the entire ELLGGP sequence (residues 233-238) was more active than wild-type IgG1. Thus, in addition to the primary contact site identified in the N terminus of the  $\gamma$ 1 **CH2 domain**, secondary sites involving residues from the C-terminal half of the domain may also contribute to the IgG1-Fc $\gamma$ RI interaction.
- L2 ANSWER 34 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN  
 1991:141190 Document No. 114:141190 The differential ability of human IgG1 and IgG4 to activate complement is determined by the carboxy-terminal sequence of the **CH2 domain**. Tao, Mi Hua; Canfield, Stephen M.; Morrison, Sherie L. (Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA). Journal of Experimental Medicine, 173(4), 1025-8 (English) 1991. CODEN: JEMEAV. ISSN: 0022-1007.
- AB Using domain switch **chimeric antibodies**, the important role is confirmed of CH2 in complement activation. The structures responsible for the differential ability of human IgG1 and IgG4 to activate complement are located at the C-terminal part (from residue 292 to 340) of the **CH2 domain**. The amino acids in CH2 that might be involved in complement interaction are discussed. While CH3 contributes to efficient complement activation, CH3 from IgG2 and CH3 IgG3 are equally effective.
- L2 ANSWER 35 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN  
 1990:511693 Document No. 113:111693 Serum half-life and tumor localization of a **chimeric antibody** deleted of the **CH2 domain** and directed against the disialoganglioside GD2. Mueller, Barbara M.; Reisfeld, Ralph A.; Gillies, Stephen D. (Dep. Immunol., Res. Inst. Scripps Clin., La Jolla, CA, 92037, USA). Proceedings of the National Academy of Sciences of the United States of America, 87(15), 5702-5 (English) 1990. CODEN: PNASA6. ISSN: 0027-8424.
- AB A chimeric human/mouse antibody was engineered to the tumor-associated antigen ganglioside GD2, with the aim of decreasing its serum half-life, maintaining its full antigen-binding capacity, and deleting its effector functions, thus making it a potentially useful reagent for the radioimaging of tumors. To this end, the constant region of the human  $\gamma$ 1 chain was mutated by deleting the second domain (CH2). The CH2-deleted antibody (ch14.18- $\Delta$ CH2) was cleared from the blood of athymic (nu/nu) mice bearing human melanoma tumors with the same kinetics as human IgG F(ab')<sub>2</sub>. At a  $\beta$  t1/2 of 12 h, 0.9% of the injected dose of 125-I-labeled ch14.18- $\Delta$ CH2 was found per mL of blood 24 h after i.v. injection. In biodistribution expts., 125I-labeled ch14.18- $\Delta$ CH2 targeted specifically to melanoma xenografts, achieving optimal tumor-to-tissue ratios 12-16 h after i.v. injection. Ch14.18- $\Delta$ CH2 was localized to the melanoma tumors more rapidly and

with better localization ratios than the intact **chimeric antibody** ch14.18. Sixteen h after i.v. injection, the tumor-to-blood and tumor-to-liver ratios of ch14.18- $\Delta$ CH2 were 5 and 12, resp., while optimal localization ratios obtained for ch14.18 were 1 and 5, resp., but 96 h after injection. A reagent such as ch14.18- $\Delta$ CH2 should be useful for radioimmuno-detection of human tumors because of reduced immunogenicity, increased targeting specificity,, and rapid clearance from circulation.

L2 ANSWER 36 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

1990:476476 Document No. 113:76476 Antibodies having modified carbohydrate content and methods of preparation and use. Morrison, Sherie L.; Oi, Vernon T.; Hinton, Paul R. (Columbia University, USA; Becton, Dickinson and Co.). Eur. Pat. Appl. EP 359096 A1 19900321, 23 pp. DESIGNATED STATES: R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1989-116368 19890905. PRIORITY: US 1988-244744 19880915.

AB A method of altering the affinity of an antibody for the antigen to which it is directed comprises introducing into the variable region of the antibody a carbohydrate recognition site under conditions such that a carbohydrate binds to the site. The carbohydrate content is also modified by deleting from a constant region of the antibody a carbohydrate recognition site which naturally occurs in the constant region. The antibodies can be labeled, attached to a solid support, or conjugated with therapeutic ligands for use in anal., affinity chromatog., and therapy. The carbohydrate site in the **CH2 domain** of human IgG subclasses was deleted by site-directed mutagenesis of the DNA encoding the IgGs. The resultant antibodies had decreased ability to bind Fc receptors and to activate complement.

=> s 12 and binding FcgRIIb

L4 0 L2 AND BINDING FCGR2B

=> s 12 and gamma receptor

L5 7 L2 AND GAMMA RECEPTOR

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PROCESSING COMPLETED FOR L5

L6 5 DUP REMOVE L5 (2 DUPLICATES REMOVED)

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L6 ANSWER 1 OF 5 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1998:778085 The Genuine Article (R) Number: 127GV. Therapy with monoclonal antibodies. II. The contribution of Fc **gamma receptor** binding and the influence of C(H)1 and C(H)3 domains on in vivo effector function. Isaacs J D (Reprint); Greenwood J; Waldmann H. St James Univ Hosp, Mol Med Unit, Clin Sci Bldg, Leeds LS9 7TF, W Yorkshire, England (Reprint); Univ Cambridge, Dept Pathol, Div Immunol, Cambridge CB2 1QP, England. JOURNAL OF IMMUNOLOGY (15 OCT 1998) Vol. 161, No. 8, pp. 3862-3869. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. Language: English. \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB An in vivo model is used to define Fe motifs engaged by mAbs to deplete target cells. Human IgG1 and human IgG4 were very potent, and mutations within a motif critical for Fc gamma R binding (glutamate 233 to proline, leucine/phenylalanine 234 to valine, and leucine 235 to alanine) completely prevented depletion, Mouse IgG2b was also potent, and mutations to prevent complement activation did not impair depletion with this isotype, as previously shown for human IgG1. In contrast, a mutation that impaired binding to mouse Fc gamma RII (glutamate 318 to alanine)

eliminated effector function of mouse IgG2b and also reduced the potency of human IgG4. To reveal potential contributions of domains other than C(H)2, domain switch mutants were created between human IgG1 and rat IgG2a. Two hybrid mAbs were generated with potencies exceeding anything previously seen in this model. While their mechanism of depletion was not defined, their activity appeared dependent upon interdomain interactions in the Pc region.

L6 ANSWER 2 OF 5 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1995:126358 The Genuine Article (R) Number: QH291. ADDITION OF A MU-TAILPIECE TO IGG RESULTS IN POLYMERIC ANTIBODIES WITH ENHANCED EFFECTOR FUNCTIONS INCLUDING COMPLEMENT-MEDIATED CYTOLYSIS BY IGG4. SMITH R I F (Reprint); COLOMA M J; MORRISON S L. UNIV CALIF LOS ANGELES, DEPT MICROBIOL & MOLEC GENET, LOS ANGELES, CA 90024; UNIV CALIF LOS ANGELES, INST MOLEC BIOL, LOS ANGELES, CA 90024. JOURNAL OF IMMUNOLOGY (1 MAR 1995) Vol. 154, No. 5, pp. 2226-2236. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The 18-amino acid carboxyl-terminal tailpiece from IgM (mu tp) has now been added to the carboxyl-termini of IgG1, IgG2, IgG3, and IgG4 constant regions to produce recombinant IgM-like IgGs. Polymeric IgCs obtained by this approach possess up to six Fcs and 12 antigen-combining sites, greatly increasing the avidity of their interactions with other molecules. Not surprisingly, the C activity of normally active IgG1 and IgG3 and somewhat less active IgG2 Abs is shown to be dramatically enhanced upon polymerization. The multiple Fcs present in a single molecule apparently allow for more efficient interactions with the multiple Clq heads present in C1, the first component of the classical C cascade. An unexpected result however, is that IgG4, normally devoid of C activity, when polymerized in the same fashion directs C-mediated lysis of target cells almost as effectively as the other polymers. Interestingly though, IgG4 mu tp does not deplete C activity in a standard consumption assay using soluble Ag. The other gamma mu tp isotypes are capable of depleting 100% of the serum lytic ability even in the absence of Ag, whereas IgG4 mu tp shows no evidence of activity in this assay under any of the conditions tested. Additionally, we show that, in contrast to monomeric IgG, polymeric IgCs bind with very high affinity to Fc **gamma receptor** II (Fc gamma RII), a low affinity receptor for wild-type antibodies; however, binding to Fc gamma RI, the high affinity receptor, appears to be unaltered. Finally, the in vivo t(1/2) of the gamma mu tp proteins is decreased relative to wild-type IgG, apparently because of rapid clearance of the polymeric fraction.

L6 ANSWER 3 OF 5 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1995:111533 The Genuine Article (R) Number: QG208. INTERACTION OF HUMAN MONOCYTE FC-GAMMA RECEPTORS WITH RAT IGG2B - A NEW INDICATOR FOR THE FC-GAMMA-RIIA (R-H131) POLYMORPHISM. HAAGEN I A (Reprint); GEERARS A J G; CLARK M R; VANDEWINKEL J G J. UNIV UTRECHT HOSP, DEPT IMMUNOL F03821, POSTBOX 85500, 3508 GA UTRECHT, NETHERLANDS (Reprint); UNIV CAMBRIDGE, DEPT PATHOL, CAMBRIDGE, ENGLAND. JOURNAL OF IMMUNOLOGY (15 FEB 1995) Vol. 154, No. 4, pp. 1852-1860. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Rat mAbs receive considerable interest for immunologic intervention in man. The rat IgG2b isotype has previously been found to be optimally active both in vivo and in vitro. We found that both a rat IgG2b CD3 mAb and a monovalent hybrid rat IgG2b-mouse IgG1 bispecific Ab triggered T cell activation in PBMC. Inhibition analyses with mAb blocking different human IgG Fc receptors (Fc gamma R) showed a dimorphic pattern. In donors expressing an Fc gamma RIIa-R/R131 allotype (previously defined on the

basis of interaction with mouse (m) IgG1 as 'high responder') anti-Fc gamma RI mAb 197 inhibited rat IgG2b induced T cell mitogenesis almost completely. In Fc gamma RIIa-H/H131 ('low responder' allotype) donors, however, both anti-Fc gamma RI mAb 197 and anti-Fc gamma RII mAb IV.3 were essential for optimal inhibition of mitogenesis. T cell proliferation experiments performed with the use of Fc gamma R-transfected fibroblasts as accessory cells showed the high affinity Fc gamma RIa (CD64) to interact with both rat IgG2b and rat IgG2b-mlgG1 hybrid CD3 mAb. The use of the two types of Fc gamma RIIa (CD32)-transfectants instead showed rat IgG2b CD3 mAb to interact solely with the IIA-H/H131 allotype. Interestingly, rat IgG2b-mlgG1 hybrid mAb did not interact effectively with this low affinity Fc gamma R. This suggests a requirement for only one rat IgG2b H chain for Fc gamma RIa-mediated binding, whereas two identical H chains seem to be necessary for proper interaction with Fc gamma RIIa. Ab-sensitized RBC-rosette experiments performed with the use of a rat IgG2b anti-NIP mAb confirmed the interaction pattern observed with rat CD3 mAb, supporting the phenomena to be isotype-, and not mAb-, dependent. These analyses point to a unique reactivity pattern for rat IgG2b Abs, interacting both with the high affinity Fc gamma RIa in all donors and Fc gamma RIIa of individuals expressing the IIA-H131 allotype.

L6 ANSWER 4 OF 5 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1992:145548 The Genuine Article (R) Number: HG033. MULTIPLE BINDING-SITES ON THE CH2 DOMAIN OF IGG FOR MOUSE FC-GAMMA-R11. LUND J (Reprint); POUND J D; JONES P T; DUNCAN A R; BENTLEY T; GOODALL M; LEVINE B A; JEFFERIS R; WINTER G. UNIV CAMBRIDGE, SCH MED, MRC, MOLEC BIOL LAB, HILLS RD, CAMBRIDGE CB2 2QH, ENGLAND; UNIV BIRMINGHAM, SCH MED, DEPT IMMUNOL, BIRMINGHAM B15 2TJ, W MIDLANDS, ENGLAND; UNIV BIRMINGHAM, DEPT BIOCHEM, BIRMINGHAM B15 2TJ, W MIDLANDS, ENGLAND. MOLECULAR IMMUNOLOGY (JAN 1992) Vol. 29, No. 1, pp. 53-59. ISSN: 0161-5890. Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB. Language: English.  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Important mammalian defensive functions such as phagocytosis are triggered in leukocytes by the interaction of the Fc region of IgG with cell surface receptors (Fc-gamma-R). The C(H) 2 domain of IgG has been implicated previously as the site of interaction with human and mouse Fc-gamma-R. This domain was mapped for interaction with mouse Fc-gamma-R11 expressed by the macrophage-like cell line P388D1, using two panels of a total of 32 site-directed mutants of mouse IgG2b and chimeric human IgG3 monoclonal antibodies. Two potential binding sites have been identified: one in or within the vicinity of the lower hinge site on IgG for human Fc-gamma-R1, and one within the binding site on IgG for Clq. The three mutant IgGs (Gly 237 --> Ala, Asn 297 --> Ala, and Glu 318 --> Ala) which do not interact in complexed form also fail to bind as monomers. A H-1 NMR study of the three non-binding monomeric mutants suggests that the mutations are largely site-specific, indicating that IgG interacts with mouse Fc-gamma-R 11 at two regions within the C(H) 2 domain. This interaction dictates phagocytosis mediated by Fc-gamma-R 11 of the P388D1 cell line.

L6 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 1  
92020986. PubMed ID: 1833770. Identification of the Fc gamma

**receptor** class I binding site in human IgG through the use of recombinant IgG1/IgG2 hybrid and point-mutated antibodies. Chappel M S; Isenman D E; Everett M; Xu Y Y; Dorrington K J; Klein M H. (Department of Immunology, University of Toronto, ON, Canada. ) Proceedings of the National Academy of Sciences of the United States of America, (1991 Oct 15) 88 (20) 9036-40. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB To characterize the region on human IgG1 responsible for its high-affinity interaction with the human Fc gamma receptor class I



(Fc gamma RI), we have analyzed the binding properties of a series of genetically engineered chimeric antinitrophenyl antibodies with identical murine antibody combining sites and hybrid IgG1/IgG2 human constant (C) regions. In addition, we have investigated a panel of reciprocally point-mutated IgG1 and IgG2 **chimeric antibodies** to identify the amino acid residues that confer cytophilic properties to human IgG1. Our data unambiguously indicate that cytophilic activity of IgG1 is an intrinsic property of its heavy-chain C region 2 (**CH2**) **domain**. We report that the entire sequence spanning residues 234-237 (LLGG) is required to restore full binding activity to IgG2 and IgG4 and that individual amino acid substitutions failed to render IgG2 active. Nevertheless, the reciprocal single point mutations in IgG1 either significantly lowered its activity or abolished it completely. Finally, we observed that an IgG2 antibody containing the entire ELLGGP sequence (residues 233-238) was more active than wild-type IgG1. This finding suggests that in addition to the primary contact site identified in the N terminus of the gamma 1 **CH2 domain**, secondary sites involving residues from the C-terminal half of the domain may also contribute to the IgG1-Fc gamma RI interaction.

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=> s l2 and reduce complement lysis
L7          0 L2 AND REDUCE COMPLEMENT LYSIS
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=> s l1 and reduce complement lysis
L8          0 L1 AND REDUCE COMPLEMENT LYSIS
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=> s l1 and complement lysis
L9          17 L1 AND COMPLEMENT LYSIS
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=> dup remove l9
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L10         6 DUP REMOVE L9 (11 DUPLICATES REMOVED)
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L10 ANSWER 1 OF 6 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
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93120172 EMBASE Document No.: 1993120172. Structural motifs involved in human IgG antibody effector functions. Greenwood J.; Clark M.; Waldmann H.. Dept of Pathology (Immunology Div), Tennis Court Road, Cambridge CB2 1QP, United Kingdom. European Journal of Immunology Vol. 23, No. 5, pp. 1098-1104 1993.
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ISSN: 0014-2980. CODEN: EJIMAF
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Pub. Country: Germany. Language: English. Summary Language: English.
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ED Entered STN: 930530
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AB A humanized IgG antibody to CAMPATH-1 antigen (CDw52) is known to be lympholytic both in vitro and in vivo. So as to improve therapeutic potency through protein engineering strategies, we wish to define the structural motifs underlying some of the documented differences in function between human (h) IgG1 and IgG4 forms of the antibody. By the creation of heavy chain domain-switch and intra-domain recombinant antibodies we have established an important role for the carboxy-terminal half of the CH2 domain in determining differential behaviour in antibody-dependent cytotoxicity (ADCC) and in complement lysis. If this same region were necessary for the effector mechanisms that operate in vivo, then it might be possible to improve antibody effector functions by construction of novel antibodies that possess within the one molecule multiple copies of the crucial hinge-CH2 associated structures. Although our previous work suggested that the hIgG4 CAMPATH-1 antibody was ineffective at ADCC, we found this to be so only in some individuals. In others, IgG4, and indeed all the IgG
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subclasses were able to mediate ADCC. Overall, though, hIgG1 remains the best choice isotype for lytic therapy in vivo.

L10 ANSWER 2 OF 6 MEDLINE on STN DUPLICATE 1

89193905. PubMed ID: 2930624. A **chimeric antibody** with dual Fc regions (bisFabFc) prepared by manipulations at the IgG hinge. Stevenson G T; Pindar A; Slade C J. (Lymphoma Research Unit, Tenovus Laboratory, General Hospital, Southampton, UK. ) Anti-cancer drug design, (1989 Mar) 3 (4) 219-30. Journal code: 8603523. ISSN: 0266-9536. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A new **chimeric antibody** for therapeutic use in human cancer is described. First the derivative FabFc was prepared by linking Fab' gamma from monoclonal antibody to Fc gamma from human normal IgG1. The bismaleimide linking agent forms a thioether bond with an SH group released by reduction of SS bonds in the hinge of each constituent. It follows that one of the original two SS bonds in the Fc hinge still has both its S atoms free, and this bond is reformed by thiol-disulphide interchange. The lone free SH in the Fc hinge can now be used to join two FabFc molecules through a similar bismaleimide linker to yield bisFabFc. As regards antibody activity against target cells, bisFabFc can be univalent, bivalent, or bispecific. Its juxtaposed dual Fc regions are designed to promote cooperative binding of effectors, and bisFabFc is indeed notably more powerful than its parent FabFc molecules in promoting **complement lysis** and antibody-dependent cellular cytotoxicity. However it is not possible at present to distinguish the separate contributions of Fc architecture, antibody affinity and other factors towards this improvement. In the present state of development a variety of FabFc against a given neoplasm may be prepared in high yield from mouse IgG1 and IgG2a antibodies, and when convenient dimerized to bisFabFc in any combination of specificities.

L10 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 2

90158552. PubMed ID: 2622456. Attack on neoplastic cell membranes by therapeutic antibody. Stevenson G T. (Lymphoma Research Unit, Tenovus Laboratory, General Hospital, Southampton, UK. ) Molecular and cellular biochemistry, (1989 Nov 23-Dec 19) 91 (1-2) 33-8. Journal code: 0364456. ISSN: 0300-8177. Pub. country: Netherlands. Language: English.

AB Mouse monoclonal antibody is not well fitted to destroying tumour cell targets. Complement and cellular effectors are inefficiently recruited, the cells can undergo antigenic modulation, antigen-negative mutants can arise, and the tumour-bearing subject can amount an immune response against the therapeutic antibody. This paper describes the preparation of two **chimeric antibody** derivatives designed to circumvent some of these problems. The first derivative is FabFc, prepared by linking Fab' gamma from monoclonal antibody to Fc gamma from human IgG. The bismaleimide linking agent forms a thioether bond with an SH group released by reduction of SS bonds in the hinge of each constituent. The second derivative is bisFabFc, formed by a bismaleimide in this case joining two FabFc molecules via a free SH in the Fc hinge of each. As regards antibody activity against target cells bisFabFc can be univalent (one active, one inactive Fab arm), bivalent, or bispecific (with each Fab arm directed against a different cell surface antigen). Its juxtaposed dual Fc regions are designed to promote cooperative binding of effectors. Some preliminary characterization in vitro has employed antibodies of anti-idiotypic specificity directed against guinea-pig L2C leukaemic B lymphocytes. The parent mouse IgG1 antibody failed to invoke complement cytotoxicity or antibody-dependent cellular cytotoxicity, while the chimeric derivatives yielded good killing in both systems. In **complement lysis** bivalent bisFabFc outperformed univalent, which in turn outperformed the FabFc monomer.

L10 ANSWER 4 OF 6 MEDLINE on STN DUPLICATE 3

89055812. PubMed ID: 3143014. Mouse/human **chimeric**

**antibodies** to a tumor-associated antigen: biologic activity of the four human IgG subclasses. Shaw D R; Khazaeli M B; LoBuglio A F. (Comprehensive Cancer Center, University of Alabama, Birmingham 35294. ) Journal of the National Cancer Institute, (1988 Dec 7) 80 (19) 1553-9. Journal code: 7503089. ISSN: 0027-8874. Pub. country: United States. Language: English.

AB Variable region genes from mouse monoclonal antibody 17-1A (gamma 2a kappa) with specificity for human gastrointestinal malignancies have been paired with human immunoglobulin constant region genes (for heavy and light chains) to produce mouse/human chimeric immunoglobulin molecules (chIgG) for each of the four human IgG subclasses. Mouse 17-1A and the four chIgG bound similarly to two human colon cancer cell lines and had comparable binding affinities. The chIgG1 and chIgG3 molecules mediated lymphocyte and monocyte antibody-dependent cell-mediated cytotoxicity (ADCC) to colon cancer tumor cell lines comparable to that of the parent murine 17-1A. The chIgG2 and chIgG4 molecules were able to mediate ADCC to colon cancer cell lines but were clearly inferior to the chIgG1 and chIgG3 reagents. None of the chIgG antibodies or the murine 17-1A was able to mediate **complement lysis** of colon cancer cell lines. These studies demonstrate the ability to produce all four human IgG subclass chimeric molecules which retain biologic activity. We have confirmed the subclass preferences of human lymphocyte and monocyte Fc receptors for human IgG subclasses previously determined by studies with monomeric or aggregated IgG. These data may aid in the selection of **chimeric antibodies** for in vivo trials.

L10 ANSWER 5 OF 6 MEDLINE on STN DUPLICATE 4  
87224133. PubMed ID: 3584980. Characterization of a mouse/human chimeric monoclonal antibody (17-1A) to a colon cancer tumor-associated antigen. Shaw D R; Khazaeli M B; Sun L K; Ghayeb J; Daddona P E; McKinney S; LoBuglio A F. Journal of immunology (Baltimore, Md. : 1950), (1987 Jun 15) 138 (12) 4534-8. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Mouse monoclonal antibody 17-1A is specific for an antigen expressed on cells of human gastrointestinal malignancies and has been used in radioimmune imaging and therapy trials for patients with colon and pancreatic cancer. The cell line SG3/5 was generated by transfection of a nonproducing mouse myeloma line (SP2/0) with a chimeric gene construct composed of variable regions from the mouse 17-1A immunoglobulin (gamma 2a, kappa) and constant regions of human k and gamma 3 immunoglobulin genes. The secreted immunoglobulin was bound by mouse monoclonal antibodies to human IgG(Fc) and IgG3 but not by staphylococcal protein A. Gel filtration HPLC profiles of purified **chimeric antibody** were similar to normal human IgG3 but quite different from native 17-1A and normal human IgG1, 2, and 4. Native and chimeric 17-1A had similar patterns of reactivity with colon cancer, other adenocarcinoma, and leukemic cell lines. Competitive inhibition documented that native and chimeric 17-1A had identical capacities to inhibit radiolabeled native 17-1A binding to colon cancer cell lines. Thus, the chimeric 17-1A exhibits molecular characteristics of normal human IgG3 but retains the specificity and binding affinity of the native 17-1A murine monoclonal antibody. The native and chimeric 17-1A mediated similar modest degrees of human lymphocyte and monocyte ADCC in a 4-hr 51Cr release assay, and both failed to mediate **complement lysis** of colon carcinoma cell lines in the presence of human complement. This human/mouse chimeric monoclonal antibody may be a good candidate for use in clinical trials because it retains the tumor antigen specificity and human effector cell recognition of the native 17-1A, would presumably have a fivefold to 10-fold longer circulating half-life in man, and should be considerably less immunogenic as compared with native murine immunoglobulins.

L10 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN

1987:532282 Document No. 107:132282 Biological properties of  
**chimeric antibodies**. Interaction with complement.  
Boulianne, Gabrielle L.; Isenman, David E.; Hozumi, Nobumichi; Shulman,  
Marc J. (Mt. Sinai Hosp., Univ. Toronto, Toronto, ON, M5G 1X5, Can.).  
Molecular Biology & Medicine, 4(1), 37-49 (English) 1987. CODEN: MBIMDG.  
ISSN: 0735-1313.

AB Genetic engineering allows the production of chimeric Igs where the same  
variable region is expressed in conjunction with constant regions of  
different species. The authors compared the capacity of mouse and  
chimeric (mouse variable region/human constant region) IgM to trigger  
complement-dependent lysis and to bind complement component C1. Guinea  
pig and human C1 were bound more efficiently by mouse IgM than by chimeric  
IgM, whereas rat and rabbit C1 were bound more efficiently by chimeric  
IgM. Comparable results were obtained for complement as measured by the  
lysis of sensitized erythrocytes. These results indicated that  
differences between the human and mouse  $\mu$  heavy chain constant regions  
define structures that are important in the C1-IgM interaction.  
Furthermore, species-specific differences in C1 also influence this  
interaction.

=> s chimeric antibod?

L11 4085 CHIMERIC ANTIBOD?

=> s l11 and reduce complement lysis

L12 0 L11 AND REDUCE COMPLEMENT LYSIS

=> s l11 and Fc mutation

L13 0 L11 AND FC MUTATION

=> s l11 and CH2 domain

L14 36 L11 AND CH2 DOMAIN

=> s treatment

L15 8751097 TREATMENT

=> s l15 and anti-CD52

L16 365 L15 AND ANTI-CD52

=> s l16 and CAMPATH-1

L17 42 L16 AND CAMPATH-1

=> s l17 and complement mediated lysis

L18 1 L17 AND COMPLEMENT MEDIATED LYSIS

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L18 ANSWER 1 OF 1 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on  
STN

2005:694837 The Genuine Article (R) Number: 940TG. Effect of alemtuzumab on  
neoplastic B cells. Golay J (Reprint); Manganini M; Rambaldi A; Introna M  
. Osped Riuniti Bergamo, Div Hematol, Lab Cellular & Gene Therapy G  
Lanzani, Presidio Matteo Rota, I-24128 Bergamo, Italy. jgolay@ospedalirium  
iti.bergamo.it. HAEMATOLOGICA (DEC 2004) Vol. 89, No. 12, pp. 1476-1483.  
ISSN: 0390-6078. Publisher: FERRATA STORTI FOUNDATION, STRADA NUOVA 134,  
27100 PAVIA, ITALY. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Background and Objectives. The therapeutic antibody alemtuzumab is  
directed against the CD52 molecule and is used for the **treatment**  
of B-cell lymphocytic leukemia (B-CLL). We investigated the mechanism of  
action of this antibody in vitro against different neoplastic B cells and  
compared it to the anti-CD20 antibody rituximab.

Design and Methods. Complement-mediated cytotoxicity assays were

performed on freshly isolated neoplastic cells using human serum as the source of Complement. Antibody-dependent cellular cytotoxicity (ADCC) was evaluated by chromium release assays, using peripheral blood mononuclear cells as effector cells, before and after 2 days of culture with interleukin-2 (IL-2).

Results. Alemtuzumab lysed cells from the 23 B-CLL samples through complement activation (mean 80%) much more efficiently than rituximab did (mean 16%), presumably because of the higher expression of CD52 than of CD20. All other leukemic B cells, including 1 prolymphocytic leukemia, 2 hairy cell leukemias and 6 B-non Hodgkin's lymphomas were effective targets for both antibodies, with 88% and 85% mean lysis, respectively. Both CD52 and CD20 were highly expressed in these cells. In contrast, most neoplastic B cell samples were poorly lysed through ADCC using freshly isolated peripheral blood mononuclear cells as effectors with either monoclonal antibody and regardless of target antigen levels. ADCC was, however, significantly increased in all cases by culturing the effector cells with IL-2 for 2 days.

Interpretation and Conclusions. **Complement-mediated lysis** is likely to be an important mechanism of action of alemtuzumab in B-CLL and combination with IL-2 may increase this antibody's efficacy through ADCC. Mature neoplastic B cells other than B-CLL express high levels of CD52 and are good targets for alemtuzumab-mediated cytotoxicity.

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PROCESSING COMPLETED FOR L17

L19 27 DUP REMOVE L17 (15 DUPLICATES REMOVED)

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L19 ANSWER 1 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2005:694837 The Genuine Article (R) Number: 940TG. Effect of alemtuzumab on neoplastic B cells. Golay J (Reprint); Manganini M; Rambaldi A; Introna M. Osped Riuniti Bergamo, Div Hematol, Lab Cellular & Gene Therapy G Lanzani, Presidio Matteo Rota, I-24128 Bergamo, Italy. jgolay@ospedalirium.iti.bergamo.it. HAEMATOLOGICA (DEC 2004) Vol. 89, No. 12, pp. 1476-1483. ISSN: 0390-6078. Publisher: FERRATA STORTI FOUNDATION, STRADA NUOVA 134, 27100 PAVIA, ITALY. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Background and Objectives. The therapeutic antibody alemtuzumab is directed against the CD52 molecule and is used for the **treatment** of B-cell lymphocytic leukemia (B-CLL). We investigated the mechanism of action of this antibody in vitro against different neoplastic B cells and compared it to the anti-CD20 antibody rituximab.

Design and Methods. Complement-mediated cytotoxicity assays were performed on freshly isolated neoplastic cells using human serum as the source of Complement. Antibody-dependent cellular cytotoxicity (ADCC) was evaluated by chromium release assays, using peripheral blood mononuclear cells as effector cells, before and after 2 days of culture with interleukin-2 (IL-2).

Results. Alemtuzumab lysed cells from the 23 B-CLL samples through complement activation (mean 80%) much more efficiently than rituximab did (mean 16%), presumably because of the higher expression of CD52 than of CD20. All other leukemic B cells, including 1 prolymphocytic leukemia, 2 hairy cell leukemias and 6 B-non Hodgkin's lymphomas were effective

targets for both antibodies, with 88% and 85% mean lysis, respectively. Both CD52 and CD20 were highly expressed in these cells. In contrast, most neoplastic B cell samples were poorly lysed through ADCC using freshly isolated peripheral blood mononuclear cells as effectors with either monoclonal antibody and regardless of target antigen levels. ADCC was, however, significantly increased in all cases by culturing the effector cells with IL-2 for 2 days.

**Interpretation and Conclusions.** Complement-mediated lysis is likely to be an important mechanism of action of alemtuzumab in B-CLL and combination with IL-2 may increase this antibody's efficacy through ADCC. Mature neoplastic B cells other than B-CLL express high levels of CD52 and are good targets for alemtuzumab-mediated cytotoxicity.

L19 ANSWER 2 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2004240154 EMBASE **Campath-1** Abs 'in the bag' for hematological malignancies: The Cape Town experience. Novitzky N.; Thomas V.; Hale G.; Waldmann H.. N. Novitzky, Division of Haematology, Univ. of Cape Town Medical School, Anzio Road, Observatory 7925 Cape Town, South Africa. *Cytotherapy* Vol. 6, No. 2, pp. 172-181 2004. Refs: 30.

ISSN: 1465-3249. CODEN: CYTRF3

Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20040628

AB Background. We examined the strategy of T-cell depletion of HLA-identical sibling grafts for the prevention of GvHD, as well as disease control and overall survival. Patients and methods. The myeloablative conditioning was radiation based. The source of stem cells was BM in 62, and cytokine-mobilized PBPC in 68 patients. GvHD prophylaxis was by ex vivo incubation of the stem-cell concentrates with Campath-1G (anti-**CD52**; n = 76) or Campath-1H (n = 54). Results. Patients receiving PBPC grafts were older (median 38.5) than those undergoing BMT (median 31; P = 0.002). More patients in the PBPC group developed chronic GvHD (p < 0.01). While no post-transplant GvHD prophylaxis was given to BMT recipients, prednisone 30 mg daily was prescribed to 12 and CYA for 90 days to a further 32 patients who had received PBPC grafts. Median follow-up was 1055 (range 28-4867) days. Although there was no difference in the survival between patients who received BMT or PBPC, death was from disease recurrence in 16 and nine (p = 0.03;  $\chi^2$  test) subjects, respectively. Multivariate analysis showed that outcome was particularly favorable in those who were given < 20 mg **Campath-1** (survival: 28/39 versus 12/29; P = 0.01, and in the subgroup of 30 patients who received Campath-1H and post-transplantation CYA. Discussion. In patients receiving BMT **Campath-1** Abs effectively prevent GvHD. For those treated with PBPC grafts, the combination of T-cell depletion and post-transplantation CYA is equally effective, without an obvious increase in disease recurrence. .COPYRGT. 2004 ISCT.

L19 ANSWER 3 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2004243331 EMBASE Sensitivity of B-cell chronic lymphocytic leukemia to Rituximab and Campath-1H and correlation with the expression of cell cycle regulatory proteins. Grdisa M.. M. Grdisa, Division of Molecular Medicine, Ruder Boskovic Institute, Bijenicka 54, 10000 Zagreb, Croatia. grdisa@irb.hr. *Croatian Medical Journal* Vol. 45, No. 2, pp. 136-141 2004.

Refs: 42.

ISSN: 0353-9504. CODEN: CMEJEN

Pub. Country: Croatia. Language: English. Summary Language: English.

ED Entered STN: 20040701

AB Aim. To assess the effect of monoclonal antibodies anti-CD20 (Rituximab)

and **anti-CD52** (Campath-1H) on the viability of B cells from patients with B cell chronic lymphocytic leukemia (B-CLL) in comparison with a cytotoxic drug fludarabine (Fluda), and to determine the influence of these agents on the expression of cell cycle regulatory proteins in vitro. **Methods.** B-CLL cells were incubated in vitro in the presence of Rituximab, Campath-1H, and Fluda. The viability of the cells was measured by MTT test (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). Gel electrophoresis and Western blotting were used to determine the effect of these agents on the expression of cell cycle regulatory proteins in vitro. **Results.** Both monoclonal antibodies, Rituximab and **Campath-1 H**, were less toxic than Fluda to B-CLL cells. Combination of Campath-1H or Rituximab with Fluda did not have a stronger effect on the cells than Fluda alone. Both antibodies decreased the expression of p27 protein and increased the expression of p23; Fluda had a similar effect. The extent of cyclin D3 and cyclin E expression did not change significantly. The expression of cyclin D2 was slightly increased in the presence of Campath-1H, but in the presence of Rituximab it either decreased slightly or remained the same. **Treatment** of B-CLL cells with Fluda alone induced significant decrease in cyclin D2 expression. **Conclusion.** These results demonstrated that monoclonal antibodies Campath-1H and Rituximab antibodies, as well as a cytotoxic drug fludarabine, had cytotoxic effects on B-CLL cells. They most likely induce apoptosis of B-CLL cells, but their activity is mediated through different pathways.

- L19 ANSWER 4 OF 27 MEDLINE on STN DUPLICATE 1  
 2003571822. PubMed ID: 12949252. Remission induction in Behcet's disease following lymphocyte depletion by the **anti-CD52** antibody **CAMPATH 1-H**. Lockwood C M; Hale G; Waldman H; Jayne D R W. (Department of Medicine, School of Clinical Medicine, University of Cambridge, UK. ) Rheumatology (Oxford, England), (2003 Dec) 42 (12) 1539-44. Electronic Publication: 2003-08-29. Journal code: 100883501. ISSN: 1462-0324. Pub. country: England: United Kingdom. Language: English.
- AB OBJECTIVE: Behcet's disease (BD) is a multisystem vasculopathy of unknown cause with variable clinical presentation and the outcome of current **treatments** is often unsatisfactory. There is evidence for T-cell autoreactivity in BD and this study explores the therapeutic response to lymphocyte depletion with a humanized **anti-CD52** antibody, **CAMPATH-1H**. **METHODS:** Eighteen patients with active BD received a single course of 134 mg of **CAMPATH-1H**. Immunosuppressives were withdrawn and prednisolone reduced according to clinical status. **Treatment** response was assessed by remission of clinical features of disease activity, erythrocyte sedimentation rate, C-reactive protein, prednisolone dose, the need for subsequent immunosuppressives and disease relapse. **RESULTS:** By 6 months, 13/18 (72%) had entered remission and average, daily prednisolone dose was reduced from 17.7 to 6.7 mg/day (P < 0.005). At patient follow-up after 37 (6-60) months, seven had relapsed after an average of 25 months, five had required the introduction of an immunosuppressive drug and two had been retreated with **CAMPATH-1H**; 10 were in stable remission and six were receiving no therapy. Moderate infusion-related adverse effects occurred in five and two developed hypothyroidism. Circulating CD4+ T cells fell to low levels after **CAMPATH-1H** and remained depressed for at least 1 yr; no opportunistic infections were seen. **CONCLUSIONS:** The therapeutic response to **CAMPATH-1H** suggests a central role for autoreactive lymphocytes in BD. The potential of **CAMPATH-1H** to induce sustained **treatment-free** remission in BD poorly controlled by conventional therapy requires further evaluation.
- L19 ANSWER 5 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN  
 2003:775814 The Genuine Article (R) Number: 717XD. **Treatment** of patients with advanced mycosis fungoides and Sezary syndrome with

alemtuzumab. Kennedy G A; Seymour J F; Wolf M; Januszewicz H; Davison J; McCormack C; Ryan G; Prince H M (Reprint). Peter MacCallum Canc Ctr, Haematol Serv, Locked Bag 1, Abeckett St, Melbourne, Vic 8006, Australia (Reprint); Peter MacCallum Canc Ctr, Haematol Serv, Melbourne, Vic 8006, Australia. EUROPEAN JOURNAL OF HAEMATOLOGY (OCT 2003) Vol. 71, No. 4, pp. 250-256. ISSN: 0902-4441. Publisher: BLACKWELL MUNKSGAARD, 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. Language: English.  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Objectives: Alemtuzumab (**anti-CD52**, Campath-1H) has recently been shown to be effective in the **treatment** of a range of hematological malignancies, including B-cell chronic lymphocytic leukemia and T-cell prolymphocytic leukemia. We undertook a phase II study to evaluate the safety, tolerability and efficacy of alemtuzumab in patients with relapsed or refractory advanced stage cutaneous T-cell lymphoma. Patients and methods: A total of eight patients were enrolled, seven with mycosis fungoides/Sezary syndrome (MF/SS) and one with large-cell transformation of MF. Seven patients had disease refractory to multiple previous therapies. Alemtuzumab (30 mg) was administered intravenously three times per week for 12 wk or until maximum response. Results: The overall response rate was 38%, with three patients achieving partial remission, two patients with stable disease and three patients with progressive disease (PD) during **treatment**. The time to progression was short, with all patients developing PD within 4 months of starting alemtuzumab. Response duration in the three PR patients was also brief, with responses lasting less than 3 months in all three cases. Significant hematological and immunosuppressive toxicity was observed, with both grade 3-4 cytopenias and significant infectious complications occurring in a majority of cases. Conclusions: Our findings suggest that in heavily pretreated, refractory, advanced stage MF/SS, although alemtuzumab has biological activity, it is associated with significant toxicity and only modest clinical utility. As such, combination regimens incorporating alemtuzumab merit further investigation in this difficult to treat patient group.

L19 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2006 ACS on STN

2003:308885 Document No. 139:51176 Therapy with monoclonal antibodies in lymphomas and chronic lymphocytic leukaemia. Rossi, J.-F. (INSERM U475 and Service d'Hematologie et d'Oncologie Medicale, Centre Hospitalier, Universitaire de Montpellier, Fr.). Retinoids & Lipid-Soluble Vitamins in Clinical Practice, 19(1), 26-31 (English) 2003. CODEN: RLVPFD. ISSN: 1367-5559. Publisher: Mediscript.

AB A review of recently developed monoclonal antibodies (MoAbs) for the **treatment** of lymphomas and lymphocytic leukemias. Rituximab mechanism of action, pharmacokinetics, antitumor activity, and safety are discussed as are radioconjugated monoclonal anti-CD20 antibodies. Other MoAbs are reviewed including **anti-CD52 Campath**  
-1.

L19 ANSWER 7 OF 27 MEDLINE on STN

DUPLICATE 2

2002713225. PubMed ID: 12476271. Alemtuzumab (Campath-1H) for **treatment** of lymphoid malignancies in the age of nonmyeloablative conditioning?. Hale G; Slavin S; Goldman J M; Mackinnon S; Giralt S; Waldmann H. (Sir William Dunn School of Pathology, University of Oxford, Oxford, UK. ) Bone marrow transplantation, (2002 Dec) 30 (12) 797-804. Ref: 74. Journal code: 8702459. ISSN: 0268-3369. Pub. country: England: United Kingdom. Language: English.

AB The **anti-CD52 (Campath-1)** monoclonal antibodies (Mabs) have a substantial history of use for controlling graft-versus-host disease in allogeneic bone marrow transplantation. Now, with the availability of a humanised form, alemtuzumab (Campath-1H), and the demonstration that this agent can reduce the tumour burden in B-CLL, a new niche may be found - as a potentially curative agent in which its tumour purging ability in vivo combines with



its role as a conditioning agent in nonmyeloablative transplantation. Review of the literature shows that alemtuzumab has unique advantages as a method of depleting malignant lymphocytes, including those in patients resistant to conventional chemotherapy. Alemtuzumab can also be used in BMT for depletion of normal T and B lymphocytes of both the recipient and donor for prevention of graft rejection and GVHD. It allows good stem cell recovery with resultant rapid engraftment, has a low risk of EBV-triggered secondary malignancy and does not interfere with blood stem cell mobilisation. As a method of eliminating the malignant clone in B-CLL, alemtuzumab has shown remarkable efficacy in heavily pre-treated patients, a number of whom have progressed to autologous or allogeneic transplantation. Efficacy data are shown within the context of other transplantation data for B-CLL. These results indicate that the combination of tumour-depleting and immunosuppressive properties of alemtuzumab should be explored, with the hope of providing improved **treatment** options for elderly patients with advanced B-CLL or indolent lymphoma whose prognosis is too poor currently to allow **treatment** with traditional regimens of high-dose myeloablative chemotherapy.

L19 ANSWER 8 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN 2003:357705 Document No.: PREV200300357705. Blood Levels of Alemtuzumab during **Treatment** of Patients with Chronic Lymphocytic Leukemia.

Comparison of Intravenous and Subcutaneous Routes of Administration. Hale, Geoff [Reprint Author]; Rebello, Peppy [Reprint Author]; Kimby, Eva [Reprint Author]; Lundin, Jeanette [Reprint Author]; Mellstedt, Hakan [Reprint Author]; Osterborg, Anders [Reprint Author]; Fegan, Chris [Reprint Author]; Leach, Mike [Reprint Author]; Brettman, Lee [Reprint Author]; Kennedy, Ben [Reprint Author]; Rawstron, Andy [Reprint Author]; Hillmen, Peter [Reprint Author]. Sir William Dunn School of Pathology, University of Oxford, Oxford, UK. Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 777. print.

Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Alemtuzumab (Campath-1H) is a humanised monoclonal **anti-**

**CD52** antibody approved for the **treatment** of chronic lymphocytic leukemia (CLL) after failure of alkylating agents and fludarabine. The standard protocol uses an intravenous (iv) dose escalated from 3 mg up to 30 mg given three times a week for up to 12 weeks. Some investigators have reported good results with similar doses given subcutaneously (sc). This is more convenient for patient and physician and has less severe systemic side effects associated with the first doses. However, the bioavailability of antibody given by the sc route had not previously been established. We used a validated flow cytometry assay to measure blood levels of alemtuzumab in two groups: 30 patients with fludarabine-refractory CLL treated according to the standard iv protocol (CAM213) and 20 patients with previously untreated CLL who received the same doses given sc for up to 18 weeks. In the iv group, samples were collected once a week before and after the dose and a set was collected for pharmacokinetic evaluation after the last dose. The highest peak samples were in the range 2.8 to 26.4 mug/ml (mean 10.7 mug/ml) whilst the highest trough samples (48 h) were in the range < 0.5 to 18.3 mug/ml (mean 5.4 mug/ml). The cumulative dose given before the antibody level reached 1 mug/ml was 13 to 316 mg (mean 90 mg). There was a wide range of terminal half lives in different patients ranging from approx 1 to 9 days. Unlike previous PK studies with alemtuzumab, the patients all had substantial tumour burden and the wide variability in antibody levels was almost certainly related to the large amount of CD52 antigen. A strong correlation was seen between antibody levels and the clinical response at the end of **treatment** as indicated by flow cytometry for minimal disease in the bone marrow. Ultimate blood levels in the sc

group were very similar to the trough levels in the iv group (0.6 to 24.8 mug/ml, mean 5.4 mug/ml). It took significantly longer for these levels to be reached and the cumulative dose before the antibody level reached 1 mug/ml was 146 to 1106 mg (mean 551 mg). However, this could represent a more effective binding to the tumour cells. There was a high proportion of good clinical responses in this group of patients, though not directly comparable with the iv group since they were previously untreated. We conclude that the sc route may be an equally good method for administration of alemtuzumab which eventually results in comparable blood levels of the drug. The possibility that blood levels may correlate with clinical response needs further investigation, both as a useful predictive clinical test, and possible as a way to further optimise the therapy.

L19 ANSWER 9 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2001183290 EMBASE Achieving optimal outcomes in chronic lymphocytic leukaemia. Hamblin T.J.. Prof. T.J. Hamblin, Department of Haematology, Royal Bournemouth Hospital, Castle Lane East, Bournemouth BH7 7DW, United Kingdom. terjoha@aol.com. Drugs Vol. 61, No. 5, pp. 593-611 2001. Refs: 156.

ISSN: 0012-6667. CODEN: DRUGAY

Pub. Country: New Zealand. Language: English. Summary Language: English.

ED Entered STN: 20010607

AB Chronic lymphocytic leukaemia (CLL) is a disease of late middle age and older. The majority of patients are diagnosed because of a lymphocytosis of at least  $5 \times 10^9/L$ , on an incidental blood count. It needs to be distinguished from mantle cell lymphoma and splenic marginal zone lymphoma by lymphocyte markers. The immunophenotype of CLL is sparse surface immunoglobulin, CD5+, CD19+, CD23+, CD79b-, and FMC7-. The disease is staged according to the presence of lymphadenopathy and/or splenomegaly and the features of bone marrow suppression. Most patients have an early stage of disease when diagnosed and perhaps 50% will never progress. This group of patients have a normal life expectancy and do not require **treatment** beyond reassurance. Progression involves an increasing white cell count, enlarging lymph nodes and spleen, anaemia and thrombocytopenia. Complications of progression include autoimmune haemolytic anaemia and thrombocytopenia, immunodeficiency, and the development of a more aggressive lymphoma. A range of prognostic factors is available to predict progression, but most haematologists rely on close observation of the patient. Intermittent chlorambucil remains the first choice **treatment** for the majority of patients. Combination chemotherapy offers no advantage. Intravenous fludarabine is probably more effective than chlorambucil, but no trial has yet shown a survival advantage for using it first rather than as a salvage **treatment** in patients not responding to chlorambucil. It is at least 40 times as expensive as chlorambucil. Cladribine may be as effective as fludarabine, although it has been used less and is even more expensive. Patients who relapse after chlorambucil should be offered retreatment with the same agent and if refractory should be switched to fludarabine, which may also be offered for retreatment on relapse. For patients refractory to both drugs, a variety of options are available. High dose corticosteroids, high dose chlorambucil, CHOP (cyclophosphamide, prednisolone, vincristine and doxorubicin), **anti-CD52**, anti-CD20 and a range of experimental drugs which are being evaluated in clinical trials. Younger patients should be offered the chance of **treatment** with curative intent, preferably in the context of a clinical trial. Autologous stem cell transplantation after achieving a remission with fludarabine has relative safety and may produce molecular complete remissions. Only time will tell whether some of these patients are cured but it seems unlikely. Standard allogeneic bone marrow transplant is probably too hazardous for most patients, but non-myeloablative regimens hold out the hope of invoking a graft-versus-leukaemia effect without a high tumour-related mortality. Trials of immunotherapy are exciting options for a few

patients in specialised centres.

L19 ANSWER 10 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2002:129991 Document No.: PREV200200129991. Sezary Syndrome responds to **treatment** with **Campath 1-H**. Foukaneli, Theodora [Reprint author]; Marsh, Judith C. W. [Reprint author]; Pettegell, Ruth [Reprint author]; Dyer, Martin; Catovsky, Daniel; Dearden, Claire E. [Reprint author]; Gordon-Smith, Edward C. [Reprint author]. Haematology, St George's Hospital Medical School, London, UK. Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 132a. print. Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Sezary Syndrome (SS) is an aggressive T cell malignancy characterised by exfoliative erythroderma with epidermotropic lymphomatous infiltration and circulating cerebriform CD4+ T cells in the peripheral blood. A variety of **treatment** modalities have been used to treat this disease with varying success. Although overall response rates are good, relapse seems to be inevitable and so far there is no evidence that any form of **treatment** is curative. Virtually all patients become refractory to conventional combination chemotherapy and new therapeutic strategies are needed. **Campath 1-H** is a humanised (IgG1) **anti CD52** monoclonal antibody which binds to the cell membrane of more than 95% of normal and malignant B and T lymphocytes, monocytes and macrophages but not on haemopoietic stem cells. It has been successfully used for the **treatment** of relapsed/refractory B-Non-Hodgkin Lymphoma, Chronic Lymphocytic Leukaemia, and post thymic T-cell malignancies such as T-Prolymphocytic Leukaemia. We report of three patients with SS, one male and two females, aged 82, 74 and 60 years. All had been resistant to prior single agent chemotherapy, such as Chlorambucil, Methotrexate and Pentostatin. The peripheral blood cell lymphocyte count was: 2.5X10<sup>9</sup>/l, 14X10<sup>9</sup>/l, and 15X10<sup>9</sup>/l. **Campath 1-H** was administered intravenously to a total dose of 100/100/450 mg. Patients also received prophylaxis with Aciclovir and Co-trimoxazole. All three patients responded to **Campath 1H**, with two Complete Responses (CRs) and one Partial Response (PR). Response duration was 27, 3 and 8 months respectively. The first patient who continues to be in CR, is also on maintenance chemotherapy with small doses of monthly Chlorambucil. One patient who relapsed after eight months received further **treatment** with **Campath 1H** and achieved a second CR with overall survival of three years from the first **treatment**. **Treatment** was tolerated well with no significant toxicities, in particular no opportunistic infections. The rarity of SS hinders the development of clinical trials and therefore information on even a small group of patients treated successfully and without significant complications may influence future **treatment** options.

L19 ANSWER 11 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2001353195 EMBASE **Campath-1H (Anti-CD52)** monoclonal antibody therapy in Lymphoproliferative disorders. Pangalis G.A.; Dimopoulou M.N.; Angelopoulou M.K.; Tsekouras Ch.; Vassilakopoulos T.P.; Vaiopoulos G.; Siakantaris M.P.. Dr. G.A. Pangalis, N. Kapod. Univ. Athens Sch. Med., 1st Department of Internal Medicine, Laikon General Hospital, 17 Aghiou Thoma St., Goudi, Athens 11527, Greece. pangalis@otenet.gr. Medical Oncology Vol. 18, No. 2, pp. 99-107 2001. Refs: 60.

ISSN: 1357-0560. CODEN: MONCEZ

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20011018

AB **Campath-1H** is a humanized monoclonal antibody targeted against the CDw52

membrane antigen of lymphocytes, which causes complement and antibody-dependent cell-mediated cytotoxicity. Campath-1H has been used in B-chronic lymphocytic leukemia (B-CLL), T-prolymphocytic leukemia (T-PLL), and low-grade non-Hodgkin's lymphoma (LGNHL). Campath-1H is administered intravenously thrice weekly for up to 12 wk, at an initial dose of 3 mg, escalated to 10 and 30 mg. The responses (complete [CR] and partial [PR]) obtained in untreated B-CLL patients are of the order of 90%. In previously treated B-CLL patients, responses are of the order of approximately 40%, with 2-4% CRs. Responses are more prominent in the blood and bone marrow compared to the lymph nodes. The median duration of response is 9-12 mo. Because of the antibody's higher activity on circulating lymphocytes, it has been used for in vivo purging of residual disease in B-CLL, followed by autologous stem-cell transplantation. In heavily pretreated advanced stage LGNHL, response is achieved only in 14% of cases with B-phenotype; a 50% response rate is noted in mycosis fungoides. In T-PLL, the CR rate is approximately 60%. Promising results have been reported in a small number of patients with refractory autoimmune thrombocytopenia of lymphoproliferative disorders. The main complications of Campath-1H **treatment** are caused by tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-6 release, usually during the first intravenous infusion, and include fever, rigor, nausea, vomiting, and hypotension responsive to steroids. These side effects are usually less severe with subsequent infusions and can be prevented by paracetamol and antihistamines. Immunosuppression resulting from normal B- and T-lymphocyte depletion is frequent, resulting in an increased risk for opportunistic infections. More clinical trials in a larger number of patients are necessary to determine the exact role and indications of Campath-1H in lymphoproliferative disorders.

L19 ANSWER 12 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2001319350 EMBASE [Immunosuppression: Ongoing clinical trials]. IMMUNOSUPPRESSION, LES ESSAIS CLINIQUES EN COURS. Rivalan J.. J. Rivalan, CHU de Rennes, Rennes, France. Presse Medicale Vol. 30, No. 24 II, pp. 38-40 1 Sep 2001.

ISSN: 0755-4982. CODEN: PRMEEM

Pub. Country: France. Language: French. Summary Language: English; French.

ED Entered STN: 20011004

AB Monoclonal antibodies: Monoclonal antibodies have been humanized to improve their duration of action and their tolerance. Lymphocyte-depleting humanized anti-CD3 antibodies are globally well tolerated. Coupled with an immunotoxin, Campath 1H, a humanized anti-CD3 antibody with specific **anti-CD52** depleting properties which also depletes immunocompetent cells, is being tested. There is increasing interest in the use of monoclonal antibodies in combination with rapamycin. Sirolimus and everolimus: The half-life of sirolimus is twice that of everolimus. Otherwise quite similar, these compounds have dosedependent side effects: leukopenia, thrombocytopenia, hyperlipidemia. There use allows a lower dosage for the calcineurin inhibitor. Sirolimus is particularly active in reducing intimal proliferation within the vessel walls. Precise indications at the present time include induction of tolerance, withdrawal of the calcineurin inhibitor, use of low-dose calcineurin inhibitor, and corticosteroid withdrawal. Eliminating the side effects of corticosteroids: Complications resulting from the use of corticosteroids, particularly bone complications, are still a problem with the low doses used in long-term regimens for transplant recipients. Several means have been proposed to reduce the risk. Total withdrawal is possible, but the risk of an increased rate of acute rejection limits indications. It appears that total withdrawal then complete abstention is not compatible immunologically. Immunosuppressors in perspective: Three groups of compounds have immunosuppressor potential: anti-adhesion molecule antibodies, costimulation blockers, and molecules inhibiting T-lymphocyte activators and their signalization factors.

- L19 ANSWER 13 OF 27 MEDLINE on STN DUPLICATE 3  
 2000468828. PubMed ID: 11022631. The Cape Town experience with haematopoietic stem cell transplantation: the paediatric programme. Roux P; Novitzky N. (University of Cape Town Leukaemia Centre, Groote Schuur Hospital, Cape Town. ) South African medical journal. Suid-Afrikaanse tydskrif vir geneeskunde, (2000 Aug) 90 (8) 804-11. Journal code: 0404520. ISSN: 0256-9574. Pub. country: South Africa. Language: English.
- AB OBJECTIVE: To determine the outcome of children with blood malignancies and bone marrow failure syndromes treated by paediatricians in the context of an adult haematopoietic transplantation programme. DESIGN: Retrospective chart review. SETTING: Hospital wards in a provincial tertiary institution in the Western Cape (Department of Haematology, Groote Schuur Hospital). SUBJECTS: Twenty-eight hospitalised children with haematological malignancies (acute lymphoblastic leukaemia (ALL) N = 4, acute myeloblastic leukaemia (AML) N = 13), or bone marrow failure syndromes (N = 11), who consecutively received autologous or allogeneic marrow grafts from HLA-identical siblings. OUTCOME MEASURES: Children (younger than 18 years) received allogeneic or autologous stem cell transplants. In the former group, two forms of graft-versus-host disease (GVHD) prophylaxis were used. Conditioning with radiation-containing regimens was followed by stem cell product infusion after T-cell depletion (CAMPATH 1, ex vivo immunoglobulin G (IgG); rat anti CD52). Children with malignancies who received unfractionated grafts were myeloablated, mainly with busulfan 16 mg/kg and cyclophosphamide 120 mg/kg. Those affected by marrow failure were prepared with cyclophosphamide and antilymphocyte globulin. Median age at time of transplantation was 116 months (range 18-212 months). The main cause of death was disease recurrence (N = 5) and GVHD (N = 3). Twenty-one children survived, 11 of 16 in complete remission (CR) from malignancy. Nine of the eleven patients presenting with marrow failure and 1 patient with severe combined immunodeficiency (SCID) remained disease free at a median follow-up of 934 days (range 70-2,330 days). Significantly longer disease-free (P = 0.03) and overall survival (P = 0.05, Cox Mantel test) was experienced by those who received T-cell-depleted stem cell grafts. CONCLUSIONS: The strategy of T-cell depletion of bone marrow/blood stem cells from HLA-matched siblings for transplantation into children with blood disorders has been successful and cost effective. These favourable results are the consequence of rational co-operation between adult and paediatric transplant physicians.
- L19 ANSWER 14 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
 2001019062 EMBASE The monoclonal antibodies Campath-1H and Rituximab in the therapy of chronic lymphocytic leukemia. Schulz H.; Winkler U.; Staak J.O.; Engert A.. Dr. H. Schulz, Klinik I fur Innere Medizin, Universitat zu Koln, Joseph-Stelzmann-Strasse 9, D-50924 Koln, Germany. Holger.Schulz@uni-koeln.de. Onkologie Vol. 23, No. 6, pp. 526-532 2000. Refs: 38. ISSN: 0378-584X. CODEN: ONKOD2 Pub. Country: Germany. Language: English. Summary Language: English; German.
- ED Entered STN: 20010201
- AB The **treatment** options for chronic lymphocytic leukemia (CLL) beside standard therapy with chlorambucil or other alkylating agents have dramatically increased in the last few years. Promising results have been reported with new cytotoxic agents such as the purine analogues fludarabine and 2-chlordeoxy-adenosine, either at first diagnosis or at relapse. Nevertheless, all patients with CLL relapse after initial response. Since residual lymphoma cells are very likely to be the origin of the clinical relapse, there is a need for new therapeutic approaches with different mechanism of action to eliminate these residual cells. These approaches include allogeneic or autologous stem cell

transplantation as well as immunotherapeutic strategies. Monoclonal antibodies, either alone or conjugated to toxins or radioisotopes, are thus being actively investigated. In clinical trials the genetically engineered chimeric unconjugated anti-CD20 antibody Rituximab and the humanized unconjugated **anti-CD52** antibody Campath-1H achieved the most promising results in the **treatment** of patients with relapsed or refractory low-grade non-Hodgkin's lymphoma. Thus far there is only little clinical experience with Rituximab in patients with CLL, and the exact role of these agent in the **treatment** of CLL has still to be determined in ongoing and future trials. As a single agent Campath-1H showed more clinical activity in previously treated CLL patients than Rituximab, with response rates of up to 33% in a multicenter pivotal study. Furthermore, the potential risks of tumor lysis and anaphylaxis for both antibodies and immunosuppression particularly for Campath-1H must be taken into account. The present review will compare the development and the basic principles of these unconjugated monoclonal antibodies and consider their present and potential role in the **treatment** of patients with CLL.

L19 ANSWER 15 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2000370421 EMBASE Monoclonal antibody therapy in lymphoid malignancies. Hainsworth J.D.. Dr. J.D. Hainsworth, Sarah Cannon Cancer Center, 250 25th Avenue North, Nashville, TN 37203, United States. jhainsworth@tnonc.com. Oncologist Vol. 5, No. 5, pp. 376-384 2000. Refs: 42.

ISSN: 1083-7159. CODEN: OCOLF6

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20001116

AB The concept of targeted therapy for patients with advanced cancer has intrigued researchers for many years. The lymphoid malignancies are particularly good candidates for this therapeutic approach, due to the identification of multiple lymphocyte-specific antigens. The recent introduction of rituximab marks the beginning of a new era in the **treatment** of lymphoid malignancies. Rituximab is one of the most active single agents for patients with refractory indolent lymphoma, producing response rates of approximately 50%, with low toxicity and a brief duration of **treatment**. Additional uses of rituximab are being evaluated in ongoing clinical trials, and are briefly reviewed. As a first-line agent, responses of approximately 70% are produced in patients with indolent lymphoma, with minimal toxicity. A substantial percentage of patients can be successfully retreated with rituximab, with second remission durations longer than the first remission (14-16 months versus 12 months). Multiple combination regimens using rituximab plus chemotherapy are also being evaluated. Although the role of these combined approaches is incompletely defined, high complete response rates can be obtained, with a higher rate of molecular complete remission (i.e., eradication of detectable bcl-2 rearrangements) than has been observed in patients receiving chemotherapy alone. Rituximab is also being evaluated in other CD20+ lymphoid malignancies including large-cell lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom's macroglobulinemia. Within the next 12 months, several additional monoclonal antibodies will be available for the **treatment** of lymphoid malignancies. These include the radioimmunoconjugates tositumomab (Bexxar) and ibritumomab (Zevalin), as well as Campath-1H (**anti-CD52**) monoclonal antibody. Early clinical data with each of these agents are also briefly reviewed.

L19 ANSWER 16 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

1999396070 EMBASE Pulsed monoclonal antibody **treatment** and autoimmune thyroid disease in multiple sclerosis. Coles A.J.; Wing M.; Smith S.; Coraddu F.; Greer S.; Taylor C.; Weetman A.; Hale G.; Chatterjee

V.K.; Waldmann H.; Compston A.. Dr. A.J. Coles, University Cambridge Neurology Unit, Box 165, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, United Kingdom. Lancet Vol. 354, No. 9191, pp. 1691-1695 13 Nov 1999.

Refs: 19.

ISSN: 0140-6736. CODEN: LANCAO

Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 19991202

AB Background. Multiple sclerosis results from T-cell-dependent inflammatory demyelination of the central nervous system. Our objective was long-term suppression of inflammation with short-term monoclonal antibody **treatment**. Methods. We depleted 95% of circulating lymphocytes in 27 patients with multiple sclerosis by means of a 5-day pulse of the humanised **anti-CD52** monoclonal antibody, Campath-1H. Clinical and haematological consequences of T-cell depletion, and in-vitro responses of patients' peripheral-blood mononuclear cells were analysed serially for 18 months after **treatment**. Findings. Radiological and clinical markers of disease activity were significantly decreased for at least 18 months after **treatment**. However, a third of patients developed antibodies against the thyrotropin receptor and carbimazole-responsive autoimmune hyperthyroidism. The depleted peripheral lymphocyte pool was reconstituted with cells that had decreased mitogen-induced proliferation and interferon gamma secretion in vitro. Interpretation. Campath-1H causes the immune response to change from the Th1 phenotype, suppressing multiple sclerosis disease activity, but permitting the generation of antibody-mediated thyroid autoimmunity.

L19 ANSWER 17 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

1999424761 EMBASE Campath IH allows low-dose cyclosporine monotherapy in 31 cadaveric renal allograft recipients. Calne R.; Moffatt S.D.; Friend P.J.; Jamieson N.V.; Bradley J.A.; Hale G.; Firth J.; Bradley J.; Smith K.G.C.; Waldmann H.. R. Calne, Department of Surgery, Douglas House Annexe, Cambridge CB2 2AH, United Kingdom. Transplantation Vol. 68, No. 10, pp. 1613-1616 27 Nov 1999.

Refs: 8.

ISSN: 0041-1337. CODEN: TRPLAU

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 19991229

AB Background. Campath 1H is a depleting, humanized **anti-CD52** monoclonal antibody that has now been used in 31 renal allograft recipients. The results have been very encouraging and are presented herein. Methods. Campath 1H was administered, intravenously, in a dose of 20 mg, on day 0 and day 1 after renal transplant. Low-dose cyclosporine (Neoral) was then initiated at 72 hr after transplant. These patients were maintained on low-dose monotherapy with cyclosporine. Results. At present, the mean follow-up is 21 months (range: 15 - 28 months). All but one patient are alive and 29 have intact functioning grafts. There have been six separate episodes of steroid-responsive rejection. One patient has had a recurrence of her original disease. Two patients have suffered from opportunistic infections, which responded to therapy. One patient has died secondary to ischemic cardiac failure. Conclusions. Campath 1H has resulted in acceptable outcomes in this group of renal allograft recipients. This novel therapy is of equal efficacy compared to conventional triple therapy, but allows the patient to be steroid-free and to be maintained on very-low-dose immunosuppressive monotherapy.

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1999088591 EMBASE Ex vivo depletion of T cells from bone marrow grafts with **CAMPATH-1** in acute leukemia: Graft-versus-host disease

and graft-versus-leukemia effect. Novitzky N.; Thomas V.; Hale G.; Waldmann H.. Dr. N. Novitzky, Department of Haematology, University of Cape Town, Medical School, Anzie Road, 7925 Cape, South Africa. novitzky@samiot.uct.ac.za. Transplantation Vol. 67, No. 4, pp. 620-626 27 Feb 1999.

Refs: 46.

ISSN: 0041-1337. CODEN: TRPLAU

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 19990428

AB Background. Preventing graft-versus-host disease (GVHD) by depletion of T lymphocytes from the stem cell graft for transplantation remains controversial, mainly because of the perceived increase in disease recurrence. Methods. We retrospectively analyzed the outcome of 50 consecutive individuals in remission of acute lymphoblastic leukemia (n=13; 8 in complete remission [CR]1) or acute myeloblastic leukemia (n=37; 33 in CR1), who had received marrow grafts from HLA-identical siblings. The conditioning regimen included six 2-Gy fractions of total body irradiation, succeeded by cyclophosphamide at 120 mg/kg (with mesna) followed by four fractions of 1.5 Gy to lymphoid areas. Bone marrow (n=38) or peripheral blood mobilized donor mononuclear cells (n=12) were exposed ex vivo to **CAMPATH-1** (IgM and complement, or IgG; **anti-CD52**) antibodies, without any further posttransplantation immunosuppression. Results. Median patient age was 31 (range 14-51) years; 12 patients were 40 or older. Thirty-two patients were male. One patient died of pulmonary hemorrhage on day 10; another died on day 29 of interstitial pneumonitis. Except for one early death, all patients engrafted. Ten (21%) of the remaining 48 who were at risk, developed GVHD. In none was it greater than grade II. Eight patients developed serious viral infections. Four died of cytomegalovirus pneumonia, adenovirus hepatitis, and human immunodeficiency. Overall, 11 patients (22%) relapsed (4 of 33 acute myeloblastic leukemia in CR1) at a median of 235 (range 46-528) days. Mean posttransplantation follow-up was 1062 (median 560; range 10-4177) days. Thirty-three patients (66%) remained disease free at a mean of 1,118 (median 1439; range 159-4,177) days. For all patients, the performance status was between 82% and 100% (median 100). Conclusion. T-cell depletion with **CAMPATH-1** effectively prevents GVHD, particularly the severe acute forms, without leading to excessive risk of relapse in acute leukemia.

L19 ANSWER 19 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

1998355567 EMBASE **CAMPATH-1H** monoclonal antibody in therapy for previously treated low- grade non-Hodgkin's lymphomas: A phase II multicenter study. Lundin J.; Osterborg A.; Brittinger G.; Crowther D.; Dombret H.; Engert A.; Epenetos A.; Gisselbrecht C.; Huhn D.; Jaeger U.; Thomas J.; Marcus R.; Nissen N.; Poynton C.; Rankin E.; Stahel R.; Uppenkamp M.; Willemze R.; Mellstedt H.. Dr. J. Lundin, Dept. of Oncology (Radiumhemmet), Karolinska Hospital, S-171 76 Stockholm, Sweden. aob@rah.ks.se. Journal of Clinical Oncology Vol. 16, No. 10, pp. 3257-3263 1998.

Refs: 23.

ISSN: 0732-183X. CODEN: JCONDN

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 19981119

AB Purpose: **CAMPATH-1H** is a human immunoglobulin G1 (IgG1) **anti-CD52** monoclonal antibody (MAB) that binds to nearly all B-cell and T-cell lymphomas. We report here the results of a multicenter phase II trial of **CAMPATH-1H** in patients with advanced, low-grade non-Hodgkin's lymphoma (NHL) who were previously treated with chemotherapy. Patients and Methods: Fifty patients who had relapsed (n = 25) after or were resistant (n = 25) to chemotherapy were treated with **CAMPATH-1H** 30 mg administered as a 2-hour intravenous (IV) infusion three times weekly for a maximum period of 12 weeks. Results: Six patients (14%) with B-cell lymphomas achieved a partial remission (PR). Patients with mycosis



fungoides appeared to respond more frequently (50%; four of eight patients, which included two complete remissions [CRs]). Lymphoma cells were rapidly eliminated from blood in 16 of 17 patients (94%). CR in the bone marrow was obtained in 32% of the patients. Lymphoma skin lesions disappeared completely in four of 10 patients and partial regression was obtained in three patients. Lymphadenopathy and splenomegaly were normalized in only 5% and 15% of patients, respectively. Lymphopenia ( $< 0.5 \times 10^9/L$ ) occurred in all patients. World Health Organization (WHO) grade IV neutropenia occurred in 14 patients (28%). Opportunistic infections were diagnosed in seven patients and nine patients had bacterial septicemia. Death related to infectious complications occurred in three patients. Conclusion: CAMPATH-1H had a significant but limited activity in patients with advanced, heavily pretreated NHL. The most pronounced effects were noted in the blood and bone marrow and in patients with mycosis fungoides. The risk for serious infectious complications needs to be considered for severely ill patients who are evaluated for CAMPATH- 1H **treatment**.

L19 ANSWER 20 OF 27 MEDLINE on STN DUPLICATE 4  
 1999069304. PubMed ID: 9824507. Cross-linking of the **CAMPATH-1** antigen (CD52) mediates growth inhibition in human B- and T-lymphoma cell lines, and subsequent emergence of CD52-deficient cells. Rowan W; Tite J; Topley P; Brett S J. (Immunology Unit, Glaxo-Wellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, UK. ) Immunology, (1998 Nov) 95 (3) 427-36. Journal code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The CAMPATH-1H (CD52) antigen is a 21 000-28 000 MW glycopeptide antigen that is highly expressed on T and B lymphocytes and is coupled to the membrane by a glycosylphosphatidylinositol (GPI) anchoring structure. The humanized CAMPATH-1H **anti-CD52** antibody is extremely effective at mediating depletion of both normal and tumorigenic lymphocytes in vivo and has been used in clinical trials for lymphoid malignancy and rheumatoid arthritis. Cross-linking GPI-anchored molecules, including CD52, on the surface of T lymphocytes in the presence of phorbol 12-myristate 13-acetate or anti-CD3, results in cellular activation. In the present study we have investigated the functional effects of cross-linking CD52 on T and B tumour cell lines. Cross-linking CD52 on either a B-cell line, Wien 133, which expresses high levels of endogenous CD52 or Jurkat T cells transfected and selected to express high levels of CD52 resulted in growth inhibition. This effect showed slower kinetics and occurred in a lower percentage of cells than growth inhibition stimulated via T- or B-cell receptors. Growth inhibition of the Wien 133 line was followed by the induction of apoptosis, which appeared independent of the Fas/Fas L pathway. Wien 133 cells surviving **anti-CD52 treatment** were selected and cloned and found to have down-regulated CD52 expression, with a characteristic biphasic pattern of 10% CD52-positive, 90% negative by fluorescence-activated cell sorter analysis. Interestingly, surface expression of other GPI-linked molecules, such as CD59 and CD55, was also down-regulated, but other transmembrane molecules such as surface IgM, CD19, CD20, HLA-DR were unaffected. The present study and previous work show that this is due to a defect in the synthesis of mature GPI precursors. Separation of CD52-positive and negative populations in vitro resulted in a rapid redistribution to the mixed population. Injection of CD52-negative cells into nude mice to form a subcutaneous tumour resulted in a substantial increase in expression of CD52. These results suggest that the defect in the Wien 133 cells is reversible, although the molecular mechanism is not clear. These observations have relevance to the clinical situation as a similar GPI-negative phenotype has been reported to occur in lymphocytes following CAMPATH-1H **treatment** in vivo.

L19 ANSWER 21 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights

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1998135552 EMBASE Levels of expression of CD52 in normal and leukemic B and T cells: Correlation with in vivo therapeutic responses to Campath-1H. Ginaldi L.; De Martinis M.; Matutes E.; Farahat N.; Morilla R.; Dyer M.J.S.; Catovsky D.. Prof. D. Catovsky, Acad. Dept. Haematology Cytogenetics, The Royal Marsden Hospital, Fulham Road, London SW3 6JJ, United Kingdom. d.catovsky@icr.ac.uk. Leukemia Research Vol. 22, No. 2, pp. 185-191 1998.

Refs: 25.

ISSN: 0145-2126. CODEN: LEREDD

S 0145-2126(97)00158-6. Pub. Country: United Kingdom. Language: English.

Summary Language: English.

ED Entered STN: 19980514

AB The CD52 antigen is expressed on most normal and neoplastic lymphoid cells. The reshaped humanized IgG1 **anti-CD52** monoclonal antibody (Campath-1H) has been used in the **treatment** of hemopoietic and non-hemopoietic diseases for its ability to induce lymphocyte depletion both in vitro and in vivo. Good activity has been shown in patients with chronic T and B cell leukemias, in particular T-prolymphocytic leukemia (T-PLL). However, the response to **treatment** is not uniform and this variability may depend on differences in the level of antigen expression on the leukemic cells. To test this hypothesis, we used quantitative flow cytometry to investigate the intensity of the expression of CD52 in 45 cases of lymphoid leukemia, 24 with B-cell chronic lymphocytic leukemia (CLL), 21 with T-PLL and 12 normal controls. Normal T lymphocytes expressed higher CD52 antigen than B lymphocytes ( $p < 0.005$ ) and the antigen was also significantly higher in T-PLL compared to CLL ( $p < 0.001$ ). Moreover, the differences in CD52 expression were somewhat higher in Campath-1H treated patients who responded than in non responders. Although other factors may play a role in the response to Campath-1H in vivo, the quantitative estimation of CD52 expression may provide a rationale for the greater response in T-PLL and help select those patients with a higher probability of responding to this therapy.

L19 ANSWER 22 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

97117157 EMBASE Document No.: 1997117157. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. Osterborg A.; Dyer M.J.S.; Bunjes D.; Pangalis G.A.; Bastion Y.; Catovsky D.; Mellstedt H.. Dr. A. Osterborg, Dept. of Oncology (Radiumhemmet), Karolinska Hospital, S-171 76 Stockholm, Sweden. aob@rah.Ks.se. Journal of Clinical Oncology Vol. 15, No. 4, pp. 1567-1574 1997.

Refs: 30.

ISSN: 0732-183X. CODEN: JCONDN

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 970527

AB Purpose: CAMPATH-1H is a human immunoglobulin G1 (IgG1) **anti-CD52** monoclonal antibody (MAb) that binds to nearly all B- and T-cell lymphomas and leukemias. We report the results of a multicenter phase II trial that used CAMPATH-1H in previously chemotherapy-treated patients with chronic lymphocytic leukemia (CLL). Materials and Methods: Twenty-nine patients who had relapsed after an initial response ( $n = 8$ ) or were refractory ( $n = 21$ ) to chemotherapy were treated with CAMPATH-1H administered as a 30-mg 2-hour intravenous (IV) infusion thrice weekly for a maximum period of 12 weeks. Results: Eleven patients (38%) achieved a partial remission (PR) and one (4%) a complete remission (CR) (response rate, 42%; 95% confidence interval [CI], 23% to 61%). Three of eight patients (38%) with a relapse and nine of 21 refractory patients (43%) responded to CAM-PATH- 1H therapy. CLL cells were rapidly eliminated from blood in 28 of 29 patients (97%). CR in the bone marrow was obtained in 36% and splenomegaly resolved completely in 32%. Lymphadenopathy was normalized in only two patients (7%). The median response duration was 12

months (range, 6 to 25+). World Health Organization (WHO) grade IV neutropenia and thrombocytopenia developed in three (10%) and two patients (7%), respectively. Neutropenia and thrombocytopenia recovered in most responding patients during continued CAMPATH-1H **treatment**. Lymphopenia ( $< 0.5 \times 10^9/L$ ) occurred in all patients. Two patients had opportunistic infections and four had bacterial septicemia. Conclusion: CAMPATH-1H had significant activity in patients with advanced and chemotherapy-resistant CLL. The most pronounced effects were noted in blood, bone marrow, and spleen. Preferential clearance of blood may allow harvesting of uncontaminated blood stem cells for use in high-dose chemotherapy protocols.

L19 ANSWER 23 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1998:62331 Document No.: PREV199800062331. Ex vivo T-cell depletion of bone marrow grafts with **campath 1** prevents graft-versus-host disease without abrogating the antileukaemic effect of transplantation. Novitzky, N. [Reprint author]; Thomas, V.; Hale, G.; Waldmann, H.. Univ. Cape Town Leukaemie Centre, Dep. Hematol., Groote Schuur Hosp., Cape Town, South Africa. Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1 PART 2, pp. 391B. print.  
Meeting Info.: Thirty-ninth Annual Meeting of the American Society of Hematology. San Diego, California, USA. December 5-9, 1997. The American Society of Hematology.  
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

L19 ANSWER 24 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

96235900 EMBASE Document No.: 1996235900. Anti-CD45 and **anti-CD52** (Campath) monoclonal antibodies effectively eliminate systemically disseminated human non-Hodgkin's lymphoma B cells in Scid mice. De Kroon J.F.E.M.; De Paus R.A.; Kluin-Nelemans H.C.; Kluin P.M.; Van Bergen C.A.M.; Munro A.J.; Hale G.; Willemze R.; Frederik Falkenburg J.H.. Department of Hematology, Leiden University Hospital, P.O. Box 9600,2300 RC Leiden, Netherlands. Experimental Hematology Vol. 24, No. 8, pp. 919-926 1996.

ISSN: 0301-472X. CODEN: EXHEBH

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 960924

AB Severe combined immunodeficient (Scid) mice inoculated with the human t(14;18)-positive B cell lines DoHH2 and BEVA develop lethal systemically disseminated lymphoma (de Kroon et al., Leukemia 8:1385, and Blood 80 [suppl 1]:436). These models were used to study the therapeutic effect of rat-anti-human CD52 (Campath-1G) or CD45 monoclonal antibodies (mAbs) on systemically disseminated tumor cells and on tumor cells present in solid tumor masses. Both mAbs were effective in inhibiting growth of systemically disseminated malignant cells. When **treatment** with **anti-CD52** or anti-CD45 mAbs at a dose of 30 µg/mouse/d for 4 days was started 24 hours after intravenous inoculation of human DoHH2 or BEVA cells, a 3-log kill of tumor cells was observed as measured by prolonged survival. After **treatment**, surviving animals injected with high numbers of BEVA cells showed tumor masses in liver, kidney, and mesenteric lymph nodes. In contrast to nontreated animals, however, only low numbers of malignant cells were found in peripheral blood, and bone marrow was free of tumor cells. Similarly, after mAb **treatment** of mice inoculated subcutaneously (sc) with DoHH2 cells, no tumor cells were found in the bone marrow, and few DoHH2 cells could be detected in the peripheral blood, spleen, liver, kidney, or lung. In contrast, tumor cells present in subcutaneous tumors and axillary lymph nodes were relatively unaffected by mAb therapy. The presence of rat immunoglobulin (Ig) could be demonstrated on surviving tumor cells. The presence of murine macrophages in areas in these tumors that were depleted of DoHH2 cells suggested that the mAb-mediated

antitumor effect observed in the Scid mouse model is mediated by cellular mechanisms. Apparently these mechanisms were not sufficient to eliminate the fast-growing tumor cells present in the protected sites. Our results indicate that **treatment** with **anti-CD52** or anti-CD45 mAbs potentially may be useful as adjuvant immunotherapy for systemically disseminated B cell lymphoma.

- L19 ANSWER 25 OF 27 MEDLINE on STN DUPLICATE 5  
96382296. PubMed ID: 8790160. Unrelated donor bone marrow transplantation for children with relapsed acute lymphoblastic leukaemia in second complete remission. Oakhill A; Pamphilon D H; Potter M N; Steward C G; Goodman S; Green A; Goulden P; Goulden N J; Hale G; Waldmann H; Cornish J M. (Royal Hospital for Sick Children, Bristol. ) British journal of haematology, (1996 Sep) 94 (3) 574-8. Journal code: 0372544. ISSN: 0007-1048. Pub. country: ENGLAND: United Kingdom. Language: English.
- AB Allogeneic sibling bone marrow transplantation (BMT) is the recommended **treatment** for relapsed childhood acute lymphoblastic leukaemia (ALL), but appropriate donors are only available in 30% of cases. Unfortunately, BMT from unrelated donors (UD) has been associated with high rates of severe graft-versus-host disease (GvHD) and transplant-related mortality (TRM). In an attempt to improve outcome in UD-BMT we have assessed the impact of T-cell depletion using **CAMPATH-1 (anti-CD52)** monoclonal antibodies in 50 consecutively referred patients with relapsed ALL in second remission. All were previously treated according to MRC protocols UKALL X and XI, and then given chemotherapy on MRC R1 from relapse until UD-BMT, 19 patients had relapsed on and 31 off therapy. Patients and donors were fully matched at HLA-A, -B, -DR and -DQ loci in 29 cases and mismatched in 21 (four mismatched for more than one antigen). Pre-transplant conditioning comprised **CAMPATH-1G**, cyclophosphamide and total body irradiation. Bone marrow was T-cell depleted in vitro using **CAMPATH-1** antibodies. Additional GvHD prophylaxis consisted of cyclosporin A (42 cases), cyclosporin plus methotrexate (four) or none (four). 47 patients engrafted. The incidence of acute GvHD was very low: two patients with grade II disease in the matched group, four with grade II-IV in the mismatched group. Only four patients have chronic GvHD. The actuarial event-free survival (EFS) at 2 years is 53%, with no significant difference between the matched and mismatched group. Further leukaemic relapse was the most important cause of failure. These results are similar to the most favourable published reports for HLA-matched sibling BMT in relapsed ALL.
- L19 ANSWER 26 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN  
95250309 EMBASE Document No.: 1995250309. Emergence of CD52-, phosphatidylinositolglycan-anchor-deficient T lymphocytes after in vivo application of Campath-1H for refractory B-cell non-Hodgkin lymphoma. Hertenstein B.; Wagner B.; Bunjes D.; Duncker C.; Raghavachar A.; Arnold R.; Heimpel H.; Schrezenmeier H.. Abteilung Innere Medizin III, Medizinische Klinik und Poliklinik, Robert Koch Strasse 8, D-89070 Ulm, Germany. Blood Vol. 86, No. 4, pp. 1487-1492 1995. ISSN: 0006-4971. CODEN: BLOOAW  
Pub. Country: United States. Language: English. Summary Language: English.
- ED Entered STN: 950912
- AB CD52 is a phosphatidylinositolglycan (PIG)-anchored glycoprotein (PIG-AP) expressed on normal T and B lymphocytes, monocytes, and the majority of B-cell non-Hodgkin lymphomas. We observed the emergence of CD52- T cells in 3 patients after intravenous **treatment** with the humanized **anti-CD52** monoclonal antibody Campath-1H for refractory B-cell lymphoma and could identify the underlying mechanism. In addition to the absence of CD52, the PIG-AP CD48 and CD59 were not detectable on the CD52- T cells in 2 patients. PIG-AP- deficient T-cell clones from both patients were established. Analysis of the mRNA of the PIG-A gene

showed an abnormal size in the T-cell clones from 1 of these patients, suggesting that a mutation in the PIG-A gene was the cause of the expression defect of PIG-AP. An escape from an immune attack directed against PIG-AP+ hematopoiesis has been hypothesized as the cause of the occurrence of PIG-AP-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and aplastic anemia. Our results support the hypothesis that an attack against the PIG-AP CD52 might lead to the expansion of a PIG-anchor-deficient cell population with the phenotypic and molecular characteristics of PNH cells.

L19 ANSWER 27 OF 27 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

97311789 EMBASE Document No.: 1997311789. Ex-vivo whole blood cultures for predicting cytokine-release syndrome: Dependence on target antigen and antibody isotype. Wing M.G.; Waldmann H.; Isaacs J.; Compston D.A.S.; Hale G.. Dr. M.G. Wing, Univ. of Cambridge Neurology Unit, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, United Kingdom. mgw1001@medschl.cam.ac.uk. Therapeutic Immunology Vol. 2, No. 4, pp. 183-190 1995.

Refs: 39.

ISSN: 0967-0149. CODEN: THIMEY

Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 971113

AB Ex-vivo whole blood assays have been evaluated for their ability to accurately predict the risk of a first-dose cytokine reaction developing in vivo following therapeutic antibody infusion. Tumour necrosis factor alpha (TNF $\alpha$ ) release was rapidly detected in cultures incubated with either **anti-CD52** antibodies of the human IgG1 or rat IgG2b isotype, and to a lesser extent with a human IgG4 isotype. Endotoxin contamination of the antibodies was not responsive for cytokine release, since polymixin B failed to inhibit cytokine release using concentrations of this antibiotic which neutralized the enhanced cytokine release seen from LPS-spiked antibody. A rat IgG2b antibody to CD45 and a human IgG1 anti-CD3 also induced significant TNF release, however, an aglycosyl anti-CD3 mutant devoid of adverse side-effects in vivo, did not result in cytokine release in vitro. Since the pattern of cytokine release seen following the clinical use of these antibodies was in good agreement with the findings of the ex- vivo whole cultures, this demonstrates the usefulness of this assay to predict cytokine release in vivo.

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(FILE 'HOME' ENTERED AT 17:32:42 ON 03 JAN 2006)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 17:33:03 ON 03 JAN 2006

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L1      4085 S CHIMERIC ANTIBOD?
L2      36 S L1 AND CH2 DOMAIN
L3      0 S L2 AND RESIDUES 231-340
L4      0 S L2 AND BINDING FCGRIIB
L5      7 S L2 AND GAMMA RECEPTOR
L6      5 DUP REMOVE L5 (2 DUPLICATES REMOVED)
L7      0 S L2 AND REDUCE COMPLEMENT LYSIS
L8      0 S L1 AND REDUCE COMPLEMENT LYSIS
L9      17 S L1 AND COMPLEMENT LYSIS
L10     6 DUP REMOVE L9 (11 DUPLICATES REMOVED)
L11     4085 S CHIMERIC ANTIBOD?
L12     0 S L11 AND REDUCE COMPLEMENT LYSIS
L13     0 S L11 AND FC MUTATION
L14     36 S L11 AND CH2 DOMAIN
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L15 8751097 S TREATMENT  
L16 365 S L15 AND ANTI-CD52  
L17 42 S L16 AND CAMPATH-1  
L18 1 S L17 AND COMPLEMENT MEDIATED LYSIS  
L19 27 DUP REMOVE L17 (15 DUPLICATES REMOVED)

=> s l15 and anti-RhD  
L20 30 L15 AND ANTI-RHD

=> s l20 and FOG1  
L21 0 L20 AND FOG1

=> dup remove l20  
PROCESSING COMPLETED FOR L20  
L22 14 DUP REMOVE L20 (16 DUPLICATES REMOVED)

=> d l22 1-14 cbib abs

L22 ANSWER 1 OF 14 MEDLINE on STN  
2005010541. PubMed ID: 15636215. [The effect of opsonins on erythrocytes' phagocytosis in the vitreous--clinical observations (Part B)]. Wplyw opsonin na fagocytoze erytrocytow znajdujacych sie w ciele szklistym--obserwacje kliniczne (Czesc B). Raczynska Krystyna; Iwaszkiewicz-Bilikiewicz Barbara. (Katedry i Kliniki Chorob Oczu Akademii Medycznej w Gdansk. ) Klinika oczna, (2004) 106 (3 Suppl) 404-6. Journal code: 0376614. ISSN: 0023-2157. Pub. country: Poland. Language: Polish.  
AB PURPOSE: We demonstrate clinical material collected during several years, which illustrates the possibilities of immunotherapy in intravitreal hemorrhages. MATERIAL AND METHODS: Immunotherapy was applied in 172 persons, Rh-positive in 174 eyes with intravitreal hemorrhages of a various etiology. The therapy consisted of injecting preparations containing IgG **anti RhD** antibodies into the vitreous. RESULTS: Visual acuity improvement has been obtained in 77.6% of eyes. CONCLUSIONS: Summing up the effects of immunotherapy of hemorrhages into the vitreous body, it is necessary to stress the simplicity of performance of the procedure, its insignificant invasions and security resulting from the application of natural, human immunoglobulin.

L22 ANSWER 2 OF 14 MEDLINE on STN DUPLICATE 1  
2004216563. PubMed ID: 15113381. Pharmacokinetics and safety of recombinant **anti-RhD** in healthy RhD-negative male volunteers. Bichler J; Spycher M O; Amstutz H-P; Andresen I; Gaede K; Miescher S. (ZLB Bioplasma AG, Wankdorfstrasse 10, CH-Berne 22, Switzerland.. johann.bichler@zlb.com) . Transfusion medicine (Oxford, England), (2004 Apr) 14 (2) 165-71. Journal code: 9301182. ISSN: 0958-7578. Pub. country: England: United Kingdom. Language: English.  
AB In this first-in-man study, we assessed the pharmacokinetics, safety and tolerability of MonoRho, a human recombinant monoclonal **anti-RhD** immunoglobulin G1 (IgG1) antibody. Eighteen RhD-negative healthy male volunteers were randomized in two groups to receive a single administration of 300 micro g of MonoRho either intravenously or intramuscularly. There were no symptoms of allergic or anaphylactic type reaction in any subject, and there was no evidence of any MonoRho-related changes in laboratory safety parameters. None of the subjects mounted a detectable immune response to MonoRho. Serum samples were obtained up to 91 days after injection to measure anti-D IgG concentrations by flow cytometry. After intramuscular administration of MonoRho, anti-D IgG concentrations gradually increased reaching peak levels after a mean of 3.4 days. After 3 weeks, the mean anti-D IgG concentrations after intravenous and intramuscular administration became virtually equal to each other and remained so thereafter. In both the **treatment** groups, the mean elimination half-life was about 18 days and thus similar to that described for plasma-derived anti-D IgG. The bioavailability of

MonoRho after intramuscular administration was estimated as 46%. The excellent tolerability and safety of MonoRho as well as its expected elimination half-life supports the continued clinical development of this compound.

L22 ANSWER 3 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN 2005:480018 Document No.: PREV200510266603. The use of anti-CD20 chimeric monoclonal antibody, rituximab in adult patients with **treatment** refractory immune thrombocytopenia. Jacoub, Jack [Reprint Author]; Mchlayeh, Wassint; Tabbara, Imad; Dave, Harish P.; Siegel, Robert; Schechter, Geraldine P.. George Washington Univ, Washington, DC USA. Blood, (NOV 16 2004) Vol. 104, No. 11, Part 2, pp. 74B. Meeting Info.: 46th Annual Meeting of the American-Society-of-Hematology. San Diego, CA, USA. December 04 -07, 2004. Amer Soc Hematol. CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Introduction: Approximately 20-30% of treated patients with immune thrombocytopenia (IT) will become resistant to standard therapy. Rituximab has been reported to be effective in nearly 50% of such patients. The following report describes our experience using rituximab as both a splenectomy-sparing and salvage intervention in a heterogenous group of IT patients. Patients and Methods: 11 patients were evaluated retrospectively. Their characteristics were as follows: median age of 44 (range 20-79); 6 were female; median IT duration was 2.8 yrs (range 1mo-17yrs); median number of prior **treatments** was 3 (range 1-8); all patients had received steroids and most, high dose immunoglobulin. Other **treatments** included anti-RhD, vincristine, danazol, cyclophosphamide, staphylococcal protein-A column, plasmapheresis, mycophenolate mofetil, cyclosporine and autologous stem cell transplantation (ASCT). 6 patients (55%) had been splenectomized. 8 patients had primary idiopathic thrombocytopenic purpura (ITP) including 2 cases of Evan's syndrome (ES) and 3 had secondary IT associated with antiphospholipid antibody syndrome (APS), cutaneous panniculitis-like T-cell lymphoma and chronic lymphocytic leukemia (CLL). The planned **treatment** was rituximab 375 mg/m<sup>2</sup> i.v. weekly x 4. A complete response (CR) was defined as a rise in platelet count > 100 X 10<sup>9</sup>/L for greater than 3 months, partial response (PR) was defined as a rise in platelet count > 50 X 10<sup>9</sup>/L and no response (NR) was defined as no change or a rise < 50 X 10<sup>9</sup>/L. Results: All patients received the 4 doses of rituximab except 1 patient who achieved CR after 1 dose. Of the 8 primary ITP patients 6 (75%) attained CR, 1 had a transient PR and 1 a NR. All 3 patients with secondary IT reached CR. Overall, 91% of patients responded and 81% had CR. 1 ITP patient was spared a splenectomy and remains in CR at 7 mos. 5 of 6 (83%) splenectomized ITP patients reached CR and the 6 had a brief PR and failed to respond to retreatment. 4 of 5 splenectomized patients remain in CR at 3, 3, 32 and 34 mos, respectively. The last patient is a 44 y/o M with ES for 17 yrs who attained a transient CR with stable hemolysis but relapsed and was retreated 6 mos later with a sustained CR for nearly 3 years while maintained on intermittent rituximab therapy. Notably, he has experienced hypogammaglobulinemia with recurrent pneumonia. The 5(th) splenectomized patient reaching CR was a 35 y/o M with ES refractory to extensive pretreatment including ASCT and had a transient PR only after rituximab. He was retreated 4 mos later and reached a sustained CR 3 mos from last dose but died from hepatic failure characterized by marked cholestasis with loss of bile ducts of unclear etiology but possibly drug related. Among those with secondary IT is a 27 y/o F with APS who responded after 1 rituximab dose and remains in CR at 12 mos. Both cases of CLL and T-cell lymphoma remain untreated for their primary disease and continue in CR at 6 and 22 mos, respectively. No characteristic predicting response was identified. Rituximab therapy was well tolerated with limited infusional reaction, fatigue and headache occurring in 3 of 10 patients. Conclusion: In contrast to published reports, 81% of our refractory IT patients treated with rituximab had durable responses. Furthermore, it appears retreatment and maintenance

therapy may be effective in refractory IT at the expense of possibly an increased risk for infection.

- L22 ANSWER 4 OF 14 MEDLINE on STN DUPLICATE 2  
2002250578. PubMed ID: 11990462. Senescent erythrocytes: factors affecting the aging of red blood cells. Biondi C; Cotorruelo C; Ensinnck A; Garcia Borrás S; Racca L; Racca A. (Department of Clinical Biochemistry, School of Biochemistry Sciences, Rosario National University, Argentina.) Immunological investigations, (2002 Feb) 31 (1) 41-50. Journal code: 8504629. ISSN: 0882-0139. Pub. country: United States. Language: English.
- AB Human red blood cells (RBC) have a well-defined lifespan of 120 days affected by many cellular parameters. The aim of the present study was to investigate through a functional assay the effect of some factors in the interaction of erythrocytes with monocytes: heat rigidification, equilibration at different pH and desialylation. We also studied the interaction between stored RBC and peripheral blood monocytes with this functional erythrophagocytosis assay. Blood samples from 30 volunteer donors were investigated. 1) Senescent (Se) and Young (Y) RBC were obtained by differential centrifugation. 2) Erythrocyte suspensions: Aliquots of each sample were subjected to the following **treatments**: a) Rigidification by heat (RRBC), b) Equilibration at different pH (5.34, 6.30, 7.33, 9.20) and c) Desialylation with neuraminidase and trypsin. The functional assay was performed incubating monocytes obtained by glass adherence with these suspensions of RBC. Whole blood samples (n = 20) were stored during different periods of time (0, 7, 14, 21, 28, 35 and 42 days). The erythrophagocytosis assay was performed during six weeks incubating isologous monocytes with RBC from every unit. Negative and positive controls were performed using non sensitized (NSRBC) and sensitized with IgG **anti-RhD** (SRBC) red cells. The percentage of active monocytes (AM) obtained were: 1) YRBC: 2.8 +/- 0.9 and SeRBC: 17.5 +/- 2.1; 2a) RRBC: 3.0 +/- 0.9; 2b) 10.9 +/- 0.9, 15.5 +/- 0.8, 3.1 +/- 1.0, 4.0 +/- 1.1; 2c) 11.1 +/- 1.4 and 3.9 +/- 1.0; SRBC 32.1 +/- 1.7 and NSRBC: 2.8 +/- 1.5. The % of AM with SeRBC was higher (p < 0.001) than those obtained with NSRBC. The data of AM with RRBC were significantly lower (p < 0.001) than those obtained with SeRBC and SBRC, indicating that heat rigidification of RBC does not increase phagocytosis by monocytes. The values of AM obtained from the suspensions of erythrocytes equilibrated at different pH indicate that the acidification of RBC increases the interaction with monocytes. The % AM with neuraminidase treated RBC was higher than those observed with YRBC and NSRBC (p < 0.001). No modifications were observed with trypsin treated RBC. These results suggest that the loss of sialic acid may be involved in the physiological phagocytosis. The values of AM of stored whole blood were: 2.3 +/- 1.3, 2.7 +/- 1.3, 4.4 +/- 1.6, 6.7 +/- 1.2, 9.6 +/- 1.0, 11.7 +/- 0.8 and 13.0 +/- 1.2. The results showed a significant increase in the % of AM as a function of the preservation time from 2,3 +/- 1,3 for the first day to 13,0 +/- 1,2 for the 42nd day (p < 0.001). The data obtained in this ex vivo model show a significant increase (p < 0.001) in the phagocytosis of RBC equilibrated at low pH, desialinized (greater than 80%) with neuraminidase and stored for over 28 days. These factors would be involved in erythrocyte removal via phagocytosis during tissular homeostasis.
- L22 ANSWER 5 OF 14 MEDLINE on STN DUPLICATE 3  
2001671407. PubMed ID: 11716963. Epitope mapping of four monoclonal antibodies specific for the human RhD antigen. Nickerson Lise; Wiersma Erik J. (Cangene Corporation, 3403 American Drive, Ontario, L4V 1T4, Mississauga, Canada.. lnickerson@cangene.com) . Immunology letters, (2002 Jan 1) 80 (1) 33-9. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.
- AB RhD is a highly immunogenic erythrocyte membrane protein, implicated in hemolytic disease of the newborn and other hemolytic disorders. **Anti-RhD** antibodies are used in the **treatment**



of such disease states. Six mutant forms of recombinant RhD were stably expressed in K562 cells, and these cells were used to investigate epitope specificities of four **anti-RhD** monoclonal antibodies (mAbs). Amino acid substitutions were made in the exofacial loops of RhD to the corresponding residues found in the related RhCE polypeptide; M169L/M170R and I172F in the third loop, F223V and E233Q in the fourth loop, and D350H and G353W/A354N in the sixth loop. Each mAb was found to have a unique fine specificity and recognized multiple distant sites within RhD. The mAbs also differed in how they recognized individual amino acids in the exofacial loops of RhD.

L22 ANSWER 6 OF 14 MEDLINE on STN DUPLICATE 4  
 2000188571. PubMed ID: 10723592. Detection of an **anti-RhD** antibody 2 years after sensitization in a patient who had undergone an allogeneic BMT. Gandini G; Franchini M; de Gironcoli M; Vassanelli A; Benedetti F; Turrini A; Benini F; Aprili G. (Servizio de Immunoematologia e Trasfusione, Ospedale Policlinico, Verona, Italy. ) Bone marrow transplantation, (2000 Feb) 25 (4) 457-9. Journal code: 8702459. ISSN: 0268-3369. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We describe an HLA matched bone marrow transplantation with minor ABO incompatibility and RhD mismatch (donor RhD negative and recipient RhD positive). GVHD appeared on day +96 and therapy with steroid and cyclosporin was started. When GVHD disappeared and immunosuppressive therapy was stopped (2 years after BMT), an **anti-RhD** antibody was detected in the patient's serum. The delayed appearance of this antibody may have been associated with the prolonged immunosuppression that was required for **treatment** of the patient's GVHD.

L22 ANSWER 7 OF 14 MEDLINE on STN DUPLICATE 5  
 2001030340. PubMed ID: 10972918. Murine monoclonal antibodies reactive with a human monoclonal **anti-RhD** antibody (BRAD-5). Walker R Y; Andrew S; Kumpel B M; Austin E B. (Manchester Blood Centre, Manchester M13 9LL, UK. ) Transfusion medicine (Oxford, England), (2000 Sep) 10 (3) 225-31. Journal code: 9301182. ISSN: 0958-7578. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BRAD-3 and BRAD-5 are human monoclonal antibodies that recognize the RhD antigen on red blood cells. Both antibodies are currently in clinical trials for use as a replacement for polyclonal **anti-RhD** in the prophylactic **treatment** of haemolytic disease of the newborn. We have produced three murine IgG1 antibodies that cause agglutination of cells sensitized with BRAD-5 and also block binding of BRAD-5 to its target antigen. Using a haemagglutination assay, these antibodies, 1D7, 2E6 and 3B1, have shown specificity for BRAD-5 as they did not bind to other monoclonal **anti-RhD** antibodies of differing specificity or derived from other donors. This assay has also been used to show a lack of reactivity with **anti-RhD** antibodies present in 198 human serum samples from 44 **anti-RhD** immune individuals. The three anti-BRAD-5 antibodies have been shown to recognize different epitopes on the BRAD-5 molecule using a blocking ELISA. These antibodies appear to recognize private idiotopes on BRAD-5 that were not detectable in RhD immune sera, and therefore they will be of use for monitoring BRAD-5 in clinical trials.

L22 ANSWER 8 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
 2001:311410 Document No.: PREV200100311410. Reproducibility of red cell pegylation on the immunocamouflage of non-ABO antigens. Scott, Mark D. [Reprint author]; Murad, Kari L. [Reprint author]. Center for Immunology and Microbial Disease, Albany Medical College, Albany, NY, USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 110b. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology.

San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

- AB Alloimmunization to non-ABO blood group antigens is a significant concern in patients requiring chronic red blood cell (RBC) transfusion therapy. Previous work in our laboratory has demonstrated that chemical modification of RBC with methoxyxypoly(ethylene glycol) (mPEG) significantly camouflages non-ABO surface antigens while maintaining normal RBC structure and function (O<sub>2</sub> delivery and deformability). However, to be a potential therapeutic option for patients at risk of alloimmunization, the immunocamouflage produced by mPEG-derivatization must be consistent between differing donors. Hence, characterization of the pegylation efficacy on RBC antigenicity in a cohort of normal individuals was examined. For these studies blood was drawn from a minimum of 5 healthy human volunteers. All samples were covalently modified with varying concentrations of cyanuric chloride activated mPEG (CmPEG; 5 kDa) or PEG-bis-(1-benzotriazolyl carbonate) (BTC-mPEG; 5 or 20 kDa). Non-ABO antigen reactivity was examined in vitro by standard slide or tube agglutination assays and quantitatively via flow cytometry studies using commercial monoclonal antibodies. All mPEGs tested on all individual RBC samples resulted in dose-dependent decreases in non-ABO antigen detection. Flow cytometry quantitation of direct monoclonal antibody binding was also significantly reduced in a dose-dependent manner following RBC derivatization with CmPEG or BTC-mPEG. For example, binding of an **anti-RhD** antibody was decreased 25, 75, and >90% over controls following derivatization with 20 kDa BTC-mPEG at concentrations of 0.6, 3 and 5 mM, respectively (n=5). Similar dose-dependent decreases were seen with RhD antibody binding following 5 kDa CmPEG and BTC-mPEG modification; i.e., decrease of 25, 50 and 75% as compared to controls at derivatization concentrations of 0.6, 2.4 and 5mM, respectively (n=5). Furthermore, other non-ABO antigens commonly involved alloimmunization (C, c, K, k, Jka, Jkb, E, e) were found to exhibit similar inter-individual dose-dependent decreases in direct antibody binding. These data demonstrate that chemical modification of RBC with various mPEGs effectively and consistently blocks antigenic and immunologic recognition of non-ABO antigens within a cohort of healthy individuals. Hence, RBC pegylation may have clinical relevance in the **treatment** of patients already alloimmunized to non-ABO antigens as well as in preventing immunologic recognition and subsequent sensitization in newly transfused patients.

L22 ANSWER 9 OF 14 MEDLINE on STN

2000093221. PubMed ID: 10627751. [Prevention, diagnosis and

**treatment** of blood group immunization during pregnancy].

Preventie, diagnostiek en behandeling van bloedgroepimmunisatie tijdens de zwangerschap. van Aken W G; Christiaens G C. (Centraal Laboratorium voor de Bloedtransfusiedienst/Sanquin, Amsterdam. ) Nederlands tijdschrift voor geneeskunde, (1999 Dec 11) 143 (50) 2507-10. Ref: 16. Journal code: 0400770. ISSN: 0028-2162. Pub. country: Netherlands. Language: Dutch.

- AB In the Netherlands last year two important policy changes were introduced to prevent haemolytic disease of the newborn: antenatal administration of **anti RhD** immunoglobulin and screening for antibodies against irregular erythrocyte antigens in all pregnant women. As the predictive value of such antibodies for the detection of hemolytic disease of the newborn is limited, it is uncertain if this measure is really cost-effective. Because blood transfusion is the most important probable cause of the immunization, and because of the clinical severity of anti-K antibodies, it is advised to give exclusively K negative blood to girls and women under the age of 45 years. In addition there is a need for a uniform protocol to deal with women who have been exposed to immunization.

L22 ANSWER 10 OF 14 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

1999431507 EMBASE [Prevention, diagnosis and **treatment** of blood group immunization during pregnancy]. PREVENTIE, DIAGNOSTIEK EN BEHANDELING VAN BLOEDGROEPIMMUNISATIE TIJDENS DE ZWANGERSCHAP. Van Aken W.G.; Christiaens G.C.M.L.. Dr. W.G. Van Aken, Ctrl. Lab. Bloedtransfusied./Sanquin, Plesmanlaan 125, 1066 CX Amsterdam, Netherlands. Nederlands Tijdschrift voor Geneeskunde Vol. 143, No. 50, pp. 2507-2510 11 Dec 1999.

Refs: 16.

ISSN: 0028-2162. CODEN: NETJAN

Pub. Country: Netherlands. Language: Dutch. Summary Language: English; Dutch.

ED Entered STN: 19991229

AB In the Netherlands last year two important policy changes were introduced to prevent haemolytic disease of the newborn: antenatal administration of **anti RhD** immunoglobulin and screening for antibodies against irregular erythrocyte antigens in all pregnant women. As the predictive value of such antibodies for the detection of hemolytic disease of the newborn is limited, it is uncertain if this measure is really cost-effective. Because blood transfusion is the most important probable cause of the immunization, and because of the clinical severity of anti-K antibodies, it is advised to give exclusively K negative blood to girls and women under the age of 45 years. In addition there is a need for a uniform protocol to deal with women who have been exposed to immunization.

L22 ANSWER 11 OF 14 MEDLINE on STN DUPLICATE 6

94318479. PubMed ID: 8043446. Erythrocyte deformability has no influence on the rate of erythrophagocytosis in vitro by autologous human monocytes/macrophages. Baerlocher G M; Schlappritzi E; Straub P W; Reinhardt W H. (Department of Internal Medicine, University of Bern, Switzerland. ) British journal of haematology, (1994 Mar) 86 (3) 629-34. Journal code: 0372544. ISSN: 0007-1048. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Erythrocytes with decreased deformability are known to be rapidly removed from the circulation by splenic macrophages. The exact mechanism is, however, not well understood. We have analysed the phagocytosis of less-deformable erythrocytes by macrophages in vitro. Human monocytes/macrophages were isolated from peripheral blood and cultured for a total time of 6 h at 37 degrees C with 5% CO2. Autologous erythrocytes of the rhesus positive donor were rigidified by heat **treatment** (47 degrees C for 1 h). The change in erythrocyte deformability was assessed with a filter aspiration technique; the membrane elastic modulus was found to be increased about 2.5-fold. For controls, untreated erythrocytes and erythrocytes incubated with **anti-RhD** -antibodies were prepared. The rate of phagocytosis during 2 h at 37 degrees C and 5% CO2 was 0.74 +/- 0.59 (erythrocytes per monocyte/macrophage) for controls, 3.58 +/- 2.72 for **anti-RhD**-loaded erythrocytes and 0.82 +/- 0.74 for heat-treated erythrocytes, respectively. We conclude that decreased erythrocytes deformability does not cause an increased rate of phagocytosis by monocytes/macrophages compared to normally deformable erythrocytes in our in vitro model. This suggests that the preferential removal of rigid cells in vivo is probably not a specific process, but is due to the increased splenic transit time of rigid erythrocytes and hence longer interaction time between erythrocytes and phagocytes.

L22 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN

1992:406007 Document No. 117:6007 Targeted immunostimulation with bispecific reagents. Romet-Lemonne, Jean Loup; Fanger, Michael W. (Medarex, Inc., USA). PCT Int. Appl. WO 9205793 A1 19920416, 21 pp. DESIGNATED STATES: W: AU, CA, JP, KR, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1991-US7283 19911004. PRIORITY: US 1990-593083 19901005.

AB Immune response against an antigen is stimulated by administering the

antigen in conjunction with a binding agent (e.g. a heteroantibody) specific for an antigen-presenting cell, e.g. a macrophage. The binding agent specifically binds a receptor of the antigen-presenting cell, such as an Fc receptor, without being blocked by the endogenous ligand for the receptor. A bispecific heteroantibody was prepared from a monoclonal antibody against human erythrocytes (mono-D, a human anti-RhD antibody) and anti-FcγRI antibody 32 (FcγRI is the high affinity Fc receptor). The heteroantibody was incubated with erythrocytes, and the heteroantibody-coated erythrocytes were then incubated with adherent monocytes (macrophages). The heteroantibody triggered internalization of the antigen by the macrophages. Enhanced tetanus toxoid presentation by directing tetanus toxoid to human FcγR is also described.

L22 ANSWER 13 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1992:365397 Document No.: PREV199294047447; BA94:47447. CHILDHOOD ANEMIA AND ITS CONTROL. MIYAZAKI S [Reprint author]. SAGA MED SCH, JPN. Asian Medical Journal, (1992) Vol. 35, No. 4, pp. 204-208. CODEN: ASMJAB. ISSN: 0004-461X. Language: ENGLISH.

AB The most characteristic anemia in children in anemia neonatorum and anemia of prematurity. The major cause of hemolytic disease of the newborn accompanied by severe jaundice in the neonatal period in Caucasians is Rh(D) incompatibility, while in Asians, including Japanese, many cases of this condition are due to ABO incompatibility. The incidence of anemia due to Rh(D) incompatibility is decreasing thanks to the development of anti-Rh(D) globulin, whereas there has been a relative increase in Rh(E) incompatibility. When phototherapy is used to treat mild cases due to ABO incompatibility, since blue light appears to exert a tearing effect on DNA, green light is being used instead. In the case of anemia of prematurity, vitamin E and erythropoietin appear to be effective in treating early anemia occurring 2 or 3 months postnatally, while iron preparations are useful in **treatment** of delayed anemia occurring 7 or 8 months after birth. Bone marrow transplantation has yielded better results in pediatric patients with severe idiopathic aplastic anemia than adult patients.

L22 ANSWER 14 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1989:254720 Document No.: PREV198936121944; BR36:121944. RHESUS ANTIBODY **TREATMENT** FOR IDIOPATHIC THROMBOCYTOPENIC PURPURA IN AN RH-NEGATIVE PATIENT. ROSSI E [Reprint author]; DAMASIO E E; CERRI R; SOGNO G; LERCARI G; INCAGLIATO M; MARMONT A. SERV CHEMOIMMUNOTERAPIA EMATOLOGICA, OSPEDALE SAN MARTINO, VLE BENEDETTO XV 10, 16132 GENOVA, ITALY. Haematologica, (1988) Vol. 73, No. 6, pp. 521-523. CODEN: HAEMAX. ISSN: 0390-6078. Language: ENGLISH.

=> s l15 and anti-Der pl

L23 0 L15 AND ANTI-DER P1

=> s l15 and allergy

L24 46167 L15 AND ALLERGY

=> s l24 and anti-Der pI

L25 0 L24 AND ANTI-DER PI

=> s l24 and 2C7

L26 0 L24 AND 2C7

=> s l15 and anti-CD3

L27 5187 L15 AND ANTI-CD3

=> s 127 and YTH12.5  
L28 1 L27 AND YTH12.5

=> d 128 cbib abs

L28 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN

1994:29350 Document No. 120:29350 **Anti-CD3** aglycosylated IgG antibody. Bolt, Sarah Louise; Clark, Michael Ronald; Gorman, Scott David; Routledge, Edward Graham; Waldmann, Herman (UK). PCT Int. Appl. WO 9319196 A1 19930930, 41 pp. DESIGNATED STATES: W: AU, CA, JP, KR, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1992-GB1933 19921021. PRIORITY: GB 1992-6422 19920324.

AB Recombinant humanized IgG antibodies to human CD3 antigen are provided which retain their antigen-binding specificities and immunosuppressive properties and yet do not induce T-cell mitogenesis in vitro, induce a reduced level of cytokine release in vivo, and maintain some Fc binding ability. The antibodies may be useful for immunosuppression, e.g. in transplant recipients, or for **treatment** of cancer. Thus, the variable regions of the heavy and  $\lambda$  light chain genes of rat anti-human CD3 antibody YTH 12.5 were cloned and reshaped by site-directed mutagenesis, and ligated with genes for human IgG1 constant regions. Substitution of Asn with Ala prevented glycosylation of the antibody during expression by CHO cells. The chimeric aglycosylated antibody blocked the mixed lymphocyte reaction, indicating that it had a reduced capacity to interact with Fc receptors on accessory cells, and induced less release of tumor necrosis factor in human CD3 transgenic mice than did the parental IgG1 antibody.

=> s 115 and graft-vs-host  
L29 10942 L15 AND GRAFT-VS-HOST

=> s 129 and chimeric antibody  
L30 23 L29 AND CHIMERIC ANTIBODY

=> dup remove 130  
PROCESSING COMPLETED FOR L30  
L31 23 DUP REMOVE L30 (0 DUPLICATES REMOVED)

=> d 131 1-23 cbib abs

L31 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:902921 Document No. 143:246762 Bispecific antibodies, **chimeric antibodies** and fragments specific to human CD3 complex and antigen or tumor antigen for diagnosis and **treatment** of cancer, inflammation, allergy, infection and autoimmune disease. Kufer, Peter; Lenkkeri-Schuetz, Ulla; Lutterbuese, Ralf; Kohleisen, Birgit (Micromet A.-G., Germany). PCT Int. Appl. WO 2005077982 A1 20050825, 94 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-EP1573 20050216. PRIORITY: EP 2004-3445 20040216.

AB The present invention provides a bispecific binding mol., wherein said mol. comprises or consists of at least two domains whereby one of said at least two domains specifically binds to/interacts with the human CD3 complex and said domain comprises an amino acid sequence of an antibody derived light chain, wherein said amino acid sequence is a particularly

identified amino acid sequence comprising specific amino acid substitutions, and a second domain is or contains at least one further antigen-interaction-site and/or at least one further effector domain. The invention further provides nucleic acid mols. encoding the bispecific binding mols. of the invention, vectors comprising said nucleic acid mols. and host cells transformed or transfected with said vectors. Moreover, the invention concerns a method for the production of bispecific binding mols. of the invention and compns. comprising the bispecific binding mols. of the invention, the nucleic acid mols. of the invention or the host cells of the invention.

L31 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:160980 Document No. 142:259980 Antibodies specific to TRAIL receptor TR-7 and conjugates for diagnosis, prognosis and **treatment** of cancer, GVHD, AIDS and neurodegenerative disease. Salcedo, Theodora; Rosen, Craig A.; Albert, Vivian R.; Humphreys, Robin; Vaughan, Tristan John (Human Genome Sciences, Inc., USA). PCT Int. Appl. WO 2005016236 A2 20050224, 342 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US13900 20040505. PRIORITY: US 2003-2003/PV46809U 20030506; US 2003-2003/PV495140 20030815.

AB The present invention relates to antibodies and related mols. that immunospecifically bind to TRAIL receptor, TR-7. Such antibodies have uses, for example, in the prevention and **treatment** of cancers and other proliferative disorders. The invention also relates to nucleic acid mols. encoding anti-TR-7 antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially cancer and other hyperproliferative disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related mols., that immunospecifically bind to TRAIL receptor TR-7.

L31 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:1050457 Document No. 143:353286 Antibodies that immunospecifically bind to TRAIL receptor TR4 for cancer diagnosis and therapy. Salcedo, Theodora W.; Ruben, Steven M.; Rosen, Craig A.; Albert, Vivian R. (Human Genome Sciences, Inc., USA). U.S. Pat. Appl. Publ. US 2005214210 A1 20050929, 156 pp., Cont.-in-part of Appl. No. PCT/03/US25457. (English). CODEN: USXXCO. APPLICATION: US 2004-986376 20041112. PRIORITY: US 2001-2001/PV29347U 20010525; US 2001-2001/PV29498U 20010604; US 2001-2001/PV30917U 20010802; US 2001-2001/PV32380U 20010921; US 2001-2001/PV32736U 20011009; US 2001-2001/PV33104U 20011107; US 2001-2001/PV33131U 20011114; US 2001-2001/PV34123U 20011220; US 2002-2002/PV36986U 20020405; US 2002-2002/139785 20020507; US 2002-2002/PV40338U 20020815; US 2002-2002/PV42573U 20021113; US 2003-2003/PV46805W 20030506; WO 2003-US25457 20030815; US 2004-2004/PV608362 20040910.

AB The present invention relates to antibodies and related mols. that immunospecifically bind to TRAIL receptor, TR4. Such antibodies have uses, for example, in the prevention and **treatment** of cancers and other proliferative disorders. The invention also relates to nucleic acid mols. encoding anti-TR4 antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially cancer

and other hyperproliferative disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related mols., that immunospecifically bind to TRAIL receptor TR4.

L31 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:1050456 Document No. 143:353285 Antibodies that immunospecifically bind to TRAIL receptor TR4 for cancer diagnosis and therapy. Salcedo, Theodora W.; Ruben, Steven M.; Rosen, Craig A.; Albert, Vivian R. (Human Genome Sciences, Inc., USA). U.S. Pat. Appl. Publ. US 2005214209 A1 20050929, 156 pp., Cont.-in-part of Appl. No. PCT/US03/25457. (English). CODEN: USXXCO. APPLICATION: US 2004-986349 20041112. PRIORITY: US 2001-2001/PV29347U 20010525; US 2001-2001/PV29498U 20010604; US 2001-2001/PV30917U 20010802; US 2001-2001/PV32380U 20010921; US 2001-2001/PV32736U 20011009; US 2001-2001/PV33104U 20011107; US 2001-2001/PV33131U 20011114; US 2001-2001/PV34123U 20011220; US 2002-2002/PV36986U 20020405; US 2002-2002/139785 20020507; US 2002-2002/PV40338U 20020815; US 2002-2002/PV42573U 20021113; US 2003-2003/PV46805W 20030506; WO 2003-US25457 20030815; US 2004-2004/PV608362 20040910.

AB The present invention relates to antibodies and related mols. that immunospecifically bind to TRAIL receptor, TR4. Such antibodies have uses, for example, in the prevention and **treatment** of cancers and other proliferative disorders. The invention also relates to nucleic acid mols. encoding anti-TR4 antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially cancer and other hyperproliferative disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related mols., that immunospecifically bind to TRAIL receptor TR4.

L31 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:1050455 Document No. 143:345342 Antibodies that immunospecifically bind to TRAIL receptor TR7/DR4, sequences for scFvs, and therapeutic and diagnostic uses. Salcedo, Theodora W.; Rosen, Craig A.; Albert, Vivian R.; Humphreys, Robin; Vaughan, Tristan (Human Genome Sciences, Inc., USA). U.S. Pat. Appl. Publ. US 2005214208 A1 20050929, 158 pp., Cont.-in-part of Appl. No. PCT/US04/013900. (English). CODEN: USXXCO. APPLICATION: US 2004-981691 20041105. PRIORITY: US 2001-2001/PV34123U 20011220; US 2002-2002/PV36987U 20020405; US 2002-2002/PV38482U 20020604; US 2002-2002/PV39659U 20020718; US 2002-2002/PV40337U 20020815; US 2002-2002/PV42573U 20021113; US 2002-2002/322673 20021219; US 2003-2003/PV46809U 20030506; US 2003-2003/PV49514W 20030815; WO 2004-US13900 20040505; US 2004-2004/PV608386 20040910.

AB The present invention relates to antibodies and related mols. that immunospecifically bind to TRAIL receptor, TR7, also known as death receptor 4 (DR4). Such antibodies have uses, for example, in the prevention and **treatment** of cancers and other proliferative disorders. The invention also relates to nucleic acid mols. encoding anti-TR7 antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially cancer and other hyperproliferative disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related mols., that immunospecifically bind to TRAIL receptor TR7.

L31 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:1050454 Document No. 143:353284 Antibodies that immunospecifically bind to TRAIL receptor TR7 for cancer diagnosis and therapy. Salcedo, Theodora

W.; Rosen, Craig A.; Albert, Vivian R.; Humphreys, Robin; Vaughan, Tristan (Human Genome Sciences, Inc., USA). U.S. Pat. Appl. Publ. US 2005214207 A1 20050929, 159 pp., Cont.-in-part of Appl. No. PCT/US04/013900. (English). CODEN: USXXCO. APPLICATION: US 2004-981673 20041105. PRIORITY: US 2001-2001/PV34123U 20011220; US 2002-2002/PV36987U 20020405; US 2002-2002/PV38482U 20020604; US 2002-2002/PV39659U 20020718; US 2002-2002/PV40337U 20020815; US 2002-2002/PV42573U 20021113; US 2002-2002/322673 20021219; US 2003-2003/PV46809U 20030506; US 2003-2003/PV49514W 20030815; WO 2004-US13900 20040505; US 2004-2004/PV608386 20040910.

AB The present invention relates to antibodies and related mols. that immunospecifically bind to TRAIL receptor, TR7. Such antibodies have uses, for example, in the prevention and **treatment** of cancers and other proliferative disorders. The invention also relates to nucleic acid mols. encoding anti-TR7 antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially cancer and other hyperproliferative disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related mols., that immunospecifically bind to TRAIL receptor TR7.

L31 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:1050452 Document No. 143:353283 Antibodies that immunospecifically bind to TRAIL receptor TR7 for cancer diagnosis and therapy. Salcedo, Theodora W.; Rosen, Craig A.; Albert, Vivian R.; Humphreys, Robin; Vaughan, Tristan (Human Genome Sciences, Inc., USA). U.S. Pat. Appl. Publ. US 2005214205 A1 20050929, 159 pp., Cont.-in-part of Appl. No. PCT/US04/013900. (English). CODEN: USXXCO. APPLICATION: US 2004-981465 20041105. PRIORITY: US 2001-2001/PV34123U 20011220; US 2002-2002/PV36987U 20020405; US 2002-2002/PV38482U 20020604; US 2002-2002/PV39659U 20020718; US 2002-2002/PV40337U 20020815; US 2002-2002/PV42573U 20021113; US 2002-2002/322673 20021219; US 2003-2003/PV46809U 20030506; US 2003-2003/PV49514W 20030815; WO 2004-US13900 20040505; US 2004-2004/PV608386 20040910.

AB The present invention relates to antibodies and related mols. that immunospecifically bind to TRAIL receptor, TR7. Such antibodies have uses, for example, in the prevention and **treatment** of cancers and other proliferative disorders. The invention also relates to nucleic acid mols. encoding anti-TR7 antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially cancer and other hyperproliferative disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related mols., that immunospecifically bind to TRAIL receptor TR7.

L31 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:524968 Document No. 143:58519 Antibodies that specifically bind to TL5, a member of the TNF ligand superfamily, sequences thereof, and therapeutic and diagnostic uses. Rosen, Craig A.; Ruben, Steven M. (Human Genome Sciences, Inc., USA). U.S. Pat. Appl. Publ. US 2005129614 A1 20050616, 78 pp., Cont.-in-part of Appl. No. PCT/US03/10956. (English). CODEN: USXXCO. APPLICATION: US 2004-943197 20040917. PRIORITY: US 2002-2002/PV37208W 20020415; WO 2003-US10956 20030410.

AB The present invention relates to antibodies and related mols. (e.g. scFv, monoclonal antibody, **chimeric antibodies**, or fragments) that specifically bind to TL5, a member of the TNF (tumor necrosis factor) ligand superfamily. In specific embodiments, the antibodies of the invention inhibit TL5 binding to a TL5 receptor (e.g., TNF receptors TR2, TR6, or LTBR). Such antibodies have uses, for



example, in the prevention and **treatment** of cancer as well as immune system diseases and disorders including autoimmune disease, rheumatoid arthritis, graft rejection, **graft vs. host** disease, and lymphadenopathy. The invention also relates to nucleic acid mols. encoding anti-TL5 antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disorder, especially cancer

as

well as immune disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies that specifically bind to TL5.

L31 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:259732 Document No. 142:334925 Antibodies specific to human TR2 proteins and conjugates for diagnosis and **treatment** of transplant rejection, autoimmune disease, infection and cancer. Rosen, Craig A.; Ruben, Steven M. (Human Genome Sciences, Inc., USA). U.S. Pat. Appl. Publ. US 2005065326 A1 20050324, 80 pp., Cont.-in-part of Appl. No. PCT/US03/10955. (English). CODEN: USXXCO. APPLICATION: US 2004-939359 20040914. PRIORITY: US 2002-2002/PV37172W 20020412; WO 2003-US10955 20030410.

AB The present invention relates to antibodies and related mols. that specifically bind to TR2 proteins. Such antibodies have uses, for example, in the prevention and **treatment** of cancers and other proliferative disorders, autoimmune disorders, immunodeficiencies and/or HSV infection. The invention also relates to nucleic acid mols. encoding anti-TR2 antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially cancer and other hyperproliferative disorders, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related mols., that specifically bind to TR2.

L31 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2005:228923 Document No. 142:315225 Human anti-M-CSF antibodies for diagnosis and **treatment** of inflammation, neurological disease, atherogenesis, cardiac disease and cancer. Bedian, Vahe; Devalaraja, Madhav Narasimha; Low, Joseph Edwin; Mobley, James Leslie; Kellermann, Sirid-Aimee; Foltz, Ian; Haak-Frendscho, Mary (Warner-Lambert Company LLC, USA; Abgenix, Inc.). Brit. UK Pat. Appl. GB 2405873 A1 20050316, 155 pp. (English). CODEN: BAXXDU. APPLICATION: GB 2004-20044 20040909. PRIORITY: US 2003-2003/PV502163 20030910.

AB Human monoclonal antibodies that specifically bind to M-CSF, and methods for their production are disclosed. The antibodies may be used in the **treatment** of M-CSF mediated diseases, such as rheumatoid arthritis and cancer. An alternative embodiment relates to humanized and **chimeric antibodies** against M-CSF. Isolated heavy and light chains derived from the human anti-M-CSF antibodies are also provided.

L31 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2004:550854 Document No. 141:105256 Humanized and **chimeric antibodies** specific to human CD20 and conjugates for diagnosing and treating cancer and autoimmune disease. Adams, Camellia W.; Chan, Andrew C.; Crowley, Craig W.; Lowman, Henry B.; Nakamura, Gerald R.; Presta, Leonard G. (Genentech, Inc., USA). PCT Int. Appl. WO 2004056312 A2 20040708, 108 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,

MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US40426 20031216. PRIORITY: US 2002-2002/PV43411U 20021216; US 2003-2003/PV526163 20031201.

AB The invention provides humanized and chimeric anti-CD20 antibodies for **treatment** of CD20 pos. malignancies and autoimmune diseases. The humanized and **chimeric antibodies** may conjugate to cytotoxic agent, isotope or toxin, and in combination with immunosuppressive or chemotherapeutic agent for the **treatment** of B cell-associated lymphoma/leukemia, autoimmune disease or transplant rejection.

L31 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2004:306417 Document No. 140:337893 Antagonists or antibodies to A33 antigens for diagnosis and therapy of immune diseases, inflammations and cancers. Ashkenazi, Avi J.; Fong, Sherman; Goddard, Audrey; Gurney, Austin L.; Napier, Mary A.; Tumas, Daniel; Van Lookeren, Menno; Wood, William I. (Genentech, Inc., USA). PCT Int. Appl. WO 2004031105 A2 20040415, 230 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US31207 20031001. PRIORITY: US 2002-2002/265542 20021003; US 2003-2003/633008 20030731.

AB The present invention relates to compns. and methods of treating and diagnosing disorders characterized the by the presence of antigens associated with inflammatory diseases and/or cancer. Antigens associated with inflammation and inflammatory diseases and cancer are identified for use as diagnostic markers and in the **treatment** of the disease. The A33 antigens STIgMA, PRO301, PRO362, PRO245, and PRO1868 are identified. Genes for the antigens were identified by screening proprietary databases for secreted proteins. Primers derived from consensus sequences were used to cloned cDNAs for the proteins. Two of the proteins, PRO301 and PRO245, inhibited vascular endothelial growth factor stimulation of endothelial cell proliferation and stimulate T cell proliferation. They are also proinflammatory and stimulate the infiltration of leukocytes into guinea pig skin.

L31 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2004:399213 Document No. 141:122270 Chimeric CD19 antibody mediates cytotoxic activity against leukemic blasts with effector cells from pediatric patients who received T-cell-depleted allografts. Lang, Peter; Barbin, Karin; Feuchtinger, Tobias; Greil, Johann; Peipp, Matthias; Zunino, Susan J.; Pfeiffer, Matthias; Handgretinger, Rupert; Niethammer, Dietrich; Fey, Georg H. (Department of Pediatric Oncology, University Children's Hospital, University of Tuebingen, Tuebingen, Germany). Blood, 103(10), 3982-3985 (English) 2004. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: American Society of Hematology.

AB Relapse is a major problem after transplantation in children with acute B-lineage leukemias, and new therapies are needed to increase graft-vs.-leukemia (GvL) effects without inducing **graft-vs.-host** disease (GvHD). Here, we studied the ability of effector cells recovered from patients after transplantation with pos.-selected stem cells from alternative donors to induce antibody-dependent cellular cytotoxicity (ADCC). For this purpose, a chimeric CD19 antibody, CD19-4G7chim, was generated. This antibody efficiently mediated ADCC against primary acute lymphoblastic leukemia

(ALL) blasts by using purified natural killer (NK) cells from healthy donors or mononuclear cells from patients as effector cells. Increased lysis was obtained after stimulation of effector cells with interleukin-2 (IL-2). ADCC was not prevented by inhibitory effects mediated by HLA class I. We propose that **treatment** with chimeric CD19 antibodies leading to ADCC by donor-derived NK cells may become a therapeutic option for the posttransplantation **treatment** of minimal residual B-lineage ALLs.

L31 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

2003:856023 Document No. 139:349660 Antibodies specific to TL5 for diagnosis, prognosis and **treatment** of cancer, immune and autoimmune disease, inflammation and lymphadenopathy. Rosen, Craig A.; Ruben, Steven M. (Human Genome Sciences, Inc., USA). PCT Int. Appl. WO 2003089575 A2 20031030, 189 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US10956 20030410. PRIORITY: US 2002-2002/PV372087 20020415.

AB The present invention relates to antibodies and related mols. (e.g. scFv, monoclonal antibody, humanized or **chimeric antibodies**, or fragments) that specifically bind to TL5. Such antibodies have uses, for example, in the prevention and **treatment** of cancer as well as immune system diseases and disorders including autoimmune disease, rheumatoid arthritis, graft rejection, **graft vs. host** disease, and lymphadenopathy. The invention also relates to nucleic acid mols. encoding anti-TL5 antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compns. for preventing, detecting, diagnosing, treating or ameliorating a disease or disorder, especially cancer as well as immune system diseases and disorders including autoimmune disease, rheumatoid arthritis, graft rejection, **graft vs. host** disease, and lymphadenopathy, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related mols., that specifically bind to TL5.

L31 ANSWER 15 OF 23 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2001:320082 Document No.: PREV200100320082. Prior therapy with anti-CD20 **chimeric antibody** (Rituximab) may decrease the risk of acute graft-versus-host disease (GVHD) in patients with non-Hodgkin's lymphoma receiving allogeneic stem cell transplantation. Ratanatharathorn, Voravit [Reprint author]; Bociek, Robert G.; Pavletic, Steven Z.; Lynch, James C.; Ferrara, James L. M. [Reprint author]; Uberti, Joseph P. [Reprint author]. Internal Medicine and Pediatrics, University of Michigan Medical Center, Ann Arbor, MI, USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 391a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology. CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Anti-CD20 **chimeric antibody** (Rituximab) is efficacious **treatment** for lymphoma expressing the CD20 antigen. B-cell depletion, resulting from rituximab **treatment**, may also potentially abrogate host B-cell antigen presentation to donor T cells, and thus diminish the risk of acute GVHD for patients undergoing allogeneic stem cell transplantation (alloSCT). To test this hypothesis,

we retrospectively studied 37 consecutive patients with non-Hodgkin's lymphoma who received alloSCT between July 1998 and June 2000. Fourteen of these 37 patients received prior rituximab therapy for their lymphoma, and the remaining 23 patients were contemporaneous patients who did not receive rituximab. Patient's ages ranged from 23 to 66, with a median of 46. Patients receiving and not receiving rituximab were balanced with respect to numbers of prior chemotherapy regimen ( $P=0.09$ ) and the durations of disease prior to transplantation (median 26 and 32 months, respectively ( $P=0.79$ )). Peripheral blood stem cells (PSC) were used in 24 out of 28 related donor transplants. All 9 unrelated-donor recipients received marrow (BM) grafts and the remaining 4 BM grafts were given to related-donor recipients. The sources of stem cells were 6BM and 17 PSC in the no-rituximab group, and 7 BM and 7 PBSC in the rituximab group ( $P=0.14$ ). This study suggests the possible role host B-cell depletion in recipients of alloSCT as prophylaxis against acute GVHD. Animal models to elucidate the role of B-cell antigen presentation in the development of acute GVHD are being evaluated. Based on this preliminary observation, a prospective study of rituximab for the prevention of acute GVHD is planned.

L31 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

1999:425461 Document No. 131:72734 Methods of treating TNF $\alpha$ -mediated disease using chimeric anti-TNF antibodies. Le, Junming; Vilcek, Jan; Dadonna, Peter; Ghrayeb, John; Knight, David; Seigal, Scott (New York University, USA; Centocor, Inc.). U.S. US 5919452 A 19990706, 88 pp., Cont.-in-part of U.S. Ser. No. 10,406, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1994-192861 19940204. PRIORITY: US 1991-670827 19910318; US 1992-853606 19920318; US 1992-943852 19920911; US 1993-10406 19930129; US 1993-13413 19930202.

AB **Treatment** of tumor necrosis factor, TNF, mediated pathologies is provided by administering anti-TNF compds., such as anti-TNF antibodies and anti-TNF peptides, which compds. are specific for tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) or tumor necrosis factor- $\beta$  (TNF $\beta$ ) and which are useful for in vivo therapy or diagnosis of TNF $\alpha$ -mediated pathologies and conditions, wherein the anti-TNF compound is selected from the group consisting of at least one of an Ig variable region, a fragment of a TNF receptor and an anti-TNF peptide, such as a structural analog of a anti-TNF antibody fragment or a TNF receptor fragment. The anti-TNF antibodies, TNF receptors and their fragments are useful for treating bacterial infection, viral infection, parasitic infection, chronic inflammatory diseases, autoimmune diseases, malignancies, and/or neurodegenerative diseases.

L31 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

1999:337180 Document No. 131:4027 Use of a soluble RT1Aa/IgG chimeric molecule to prevent the cytotoxic effects of preformed anti-donor antibodies. Scherer, Marcus N.; Graeb, C.; Knechtle, S. J.; Jauch, K.-W.; Geissler, E. K. (Department Clinical Laboratory Sciences, Univ. South Alabama, Mobile, AL, USA). Chirurgisches Forum fuer Experimentelle und Klinische Forschung 423-426 (German) 1999. CODEN: CFEKA7. ISSN: 0303-6227. Publisher: Springer-Verlag.

AB Currently there is no reliable **treatment** for hyperacute rejection in presensitized patients. The problem with transplanting an organ to a recipient with preformed anti-donor antibodies is that the organ is at a high risk for destruction via complement-mediated cell cytotoxicity. To address this problem the authors have initiated expts. in the rat system to attempt to block anti-donor antibodies with a genetically engineered soluble chimeric MHC class I/IgG mol. The divalent rat MHC class I-like mol. consists of RT1.Aa extracellular domains ( $\alpha 1$ - $\alpha 3$ ) bound to each of the 2 variable regions of an intact IgG1 heavy-chain. The authors show, using complement-mediated cell cytotoxicity assays, that nanomolar concns. of purified soluble RT1.Aa/IgG chimeric mols. were able to greatly reduce the cytotoxic effects of serum

containing high concns. of anti-RT1.Aa antibody. These results suggest that chimeric MHC class I/IgG mols. may be potentially useful to neutralize the damaging effects of anti-donor antibody in presensitized recipients.

L31 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

1998:323159 Document No. 129:27008 Identification of unique binding interactions between certain antibodies and the human b7.1 and b7.2 co-stimulatory antigens. Anderson, Darrell R.; Hanna, Nabil; Brams, Peter (Idec Pharmaceuticals Corporation, USA). PCT Int. Appl. WO 9819706 A1 19980514, 87 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US19906 19971029. PRIORITY: US 1996-746361 19961108.

AB The present invention relates to the identification of antibodies which are specific to human B7.1 antigen (CD80) and which are capable of inhibiting the binding of B7.1 to a CD28 receptor and which are not capable of inhibiting the binding of B7.1 to a CTLA-4 receptor. Two of these antibodies, 16C10 and 7C10, significantly inhibit the production of IL-2, in spite of the existence of a second activating ligand B7.2 (CD86). Blocking of the primary activation signal between CD28 and B7.1 (CD80) with these antibodies while allowing the unimpaired or coincident interaction of CTLA-4 and B7.1 and/or B7.2 represents a combined antagonistic effect on pos. co-stimulation with an agonistic effect on neg. signalling. These antibodies may be used as specific immunosuppressants, e.g., for the **treatment** of autoimmune diseases and to prevent organ transplant rejection.

L31 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

1996:380154 Document No. 125:56235 Binding agents for **treatment** of inflammatory, autoimmune or allergic diseases. Bonnefoy, Jean-Yves Marcel Paul; Lecoanet-Henchoz, Sybille (Glaxo Group Limited, UK). PCT Int. Appl. WO 9612742 A1 19960502, 51 pp. DESIGNATED STATES: W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1995-EP4110 19951020. PRIORITY: GB 1994-21463 19941025; GB 1995-12480 19950620; GB 1995-13415 19950630.

AB Binding agents to CD11b, CD11c, CD21, CD23, a 70 to 85 KDa protein expressed on endothelial cells or a 115 KDa protein expressed on endothelial cells, can be useful in the **treatment** of inflammatory, autoimmune or allergic disease. The binding agent is a humanized antibody or fragment. Demonstrated in examples were CD23-liposomes bind to CD14+ mononuclear cells and  $\alpha$  chain of CD11b/CD18 and CD11c/CD18 recombinant transfectants, anti-CD11b and anti-CD11c monoclonal antibodies decrease CD23-liposome binding to activated blood monocytes, increases of monocyte nitrate production, oxidative burst and cytokine production by binding recombinant CD23 to CD11b and CD11c, competition of CD23-liposomes with Epstein-Barr virus, interferon  $\alpha$ , C3 peptide and C3d,g, etc.

L31 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

1996:380155 Document No. 125:31943 Binding agents to CD23. Bonnefoy, Jean-Yves Marcel Paul (Glaxo Group Limited, UK). PCT Int. Appl. WO 9612741 A1 19960502, 50 pp. DESIGNATED STATES: W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ; RW: AT, BE, BF, BJ, CF, CG, CH, CI,

CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1995-EP4109 19951020. PRIORITY: GB 1994-21463 19941025; GB 1995-12480 19950620; GB 1995-13415 19950630.

AB Binding agents to CD23 useful in the **treatment** of inflammatory, autoimmune or allergic diseases. The binding agent is a humanized antibody or fragment. Demonstrated in examples were preventative **treatment** of mice against arthritis using monoclonal anti-CD23 antibody, CD23-liposomes bind to CD14+ mononuclear cells and  $\alpha$  chain of CD11b/CD18 and CD11c/CD18 recombinant transfectants, anti-CD11b and anti-CD11c monoclonal antibodies decrease CD23-liposome binding to activated blood monocytes, increases of monocyte nitrate production, oxidative burst and cytokine production by binding recombinant CD23 to CD11b and CD11c, etc.

L31 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

1993:37480 Document No. 118:37480 Monoclonal and **chimeric antibodies** specific for human tumor necrosis factor. Le, Junming; Vilcek, Jan; Daddona, Peter E.; Ghraieb, John; Knight, David M.; Siegel, Scott A. (New York University, Can.; Centocor, Inc.). PCT Int. Appl. WO 9216553 A1 19921001, 105 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US2190 19920318. PRIORITY: US 1991-670827 19910318.

AB High-affinity mouse monoclonal antibody A2 to human tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) is prepared which binds to a neutralizing epitope on human TNF $\alpha$ . A **chimeric antibody** (cA2) containing a TNF $\alpha$ -binding variable region from A2 and a constant region from a human Ig is prepared by recombinant DNA technol. Antibodies A2 and cA2 can be used in diagnostic methods for detecting TNF $\alpha$  in pathol. conditions associated with TNF $\alpha$  production, and for removing TNF $\alpha$  from body fluids. The human-specific properties of cA2 allow its addnl. use in vivo to neutralize human TNF $\alpha$  without eliciting an immune response.

L31 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2006 ACS on STN

1992:406017 Document No. 117:6017 Antibody production by CHO cells cotransfected with vectors expressing heavy and light chains. Page, Martin John (Wellcome Foundation Ltd., UK). Eur. Pat. Appl. EP 481790 A2 19920422, 19 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1991-309595 19911017. PRIORITY: GB 1990-22543 19901017.

AB Antibody-producing CHO cell lines are prepared by cotransfection with a vector capable of expressing the light chain and another capable of expressing the heavy chain, wherein the vectors contain independently selectable markers. The light and heavy chain genes may constitute genomic DNA or preferably cDNA; the use of the same regulatory elements for both chains is preferred so that their expression is substantially balanced. In cotransfection of a CHO cell line, the vector DNAs are often integrated into the cell chromosome at the same locus; thus, the use of only 1 of the selectable markers as the basis for amplification normally results in a parallel increase in the copy number of both genes. Preferred selectable markers for amplification are dhfr (for dehydrofolate reductase; amplification with increasing concns. of methotrexate) and GS (glutamine synthetase; amplification with methionine sulfoximine). Antibodies, including altered or **chimeric antibodies**, produced by the CHO cells can be used for immunosuppression or for **treatment** of T-cell-mediated disorders, cancer, or infectious diseases. Thus, procedures for cloning the heavy and light chain cDNAs for rat monoclonal antibody Campath-1G, construction of vectors, and expression of Campath-1G in dhfr- CHO cell line DUK-B11 were described. The antibody was rapidly synthesized and secreted by the cells, even under stationary growth conditions.

L31 ANSWER 23 OF 23 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1992:253520 The Genuine Article (R) Number: HN012. IMMUNE RECEPTORS - TARGETS FOR THERAPY OF LEUKEMIA LYMPHOMA, AUTOIMMUNE-DISEASES AND FOR THE PREVENTION OF ALLOGRAFT-REJECTION. WALDMANN T A (Reprint). NCI, METAB BRANCH, BETHESDA, MD 20892 (Reprint). ANNUAL REVIEW OF IMMUNOLOGY (1992) Vol. 10, pp. 675-704. ISSN: 0732-0582. Publisher: ANNUAL REVIEWS INC, 4139 EL CAMINO WAY, PO BOX 10139, PALO ALTO, CA 94303-0139. Language: English. \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Immune receptor-directed therapy has been applied clinically to an array of human disorders. However, effective therapy using unmodified murine monoclonal antibodies was elusive because these antibodies are immunogenic and elicit a human immune response, are not cytotoxic against human cells, and in most cases are not directed against a cell surface structure required for proliferation and survival. Recently therapy mediated by monoclonal antibodies has been revolutionized by the definition of cell surface structures as targets for effective monoclonal antibody action, the creation by genetic engineering of less immunogenic and more effective monoclonal antibodies, and by the arming of such antibodies with toxins and radionuclides. Furthermore, other therapeutic agents directed toward immune receptors have been developed, including cytokine-toxin fusion proteins as alternative vehicles to address abnormal receptor-expressing cells, soluble immune receptors and naturally occurring receptor antagonists as immunomodulators, and T cell antigen receptor peptides as immunogens to provide protection against autoimmune diseases. Thus, the new insights concerning the structure and function of lymphocyte cell surface receptors and the development of different modalities of receptor-specific therapy are providing new perspectives for the treatment of human leukemia/lymphoma, autoimmune and graft-vs-host diseases, and for the prevention of allograft rejection.

=> s reduce complement lysis

L32 0 REDUCE COMPLEMENT LYSIS

=> s complement mediated lysis

L33 3376 COMPLEMENT MEDIATED LYSIS

=> s l33 and chimera?

L34 112 L33 AND CHIMER?

=> s l34 and Fc

L35 25 L34 AND FC

=> s l35 and CH2 domain

L36 2 L35 AND CH2 DOMAIN

=> dup remove l36

PROCESSING COMPLETED FOR L36

L37 2 DUP REMOVE L36 (0 DUPLICATES REMOVED)

=> d l37 1-2 cbib abs

L37 ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2001:372763 Document No.: PREV200100372763. Lysine 322 in the human IgG3

CH2 domain is crucial for antibody dependent complement activation. Thommesen, John E.; Michaelsen, Terje E.; Loset, Geir Age; Sandlie, Inger [Reprint author]; Brekke, Ole H.. Department of Biology, Division of Molecular Cell Biology, University of Oslo, 0316, Oslo, Blindern, Norway. inger.sandlie@bio.uio.no. Molecular Immunology, (Novmeber, 2000) Vol. 37, No. 16, pp. 995-1004. print.

CODEN: MOIMD5. ISSN: 0161-5890. Language: English.

AB The classical complement activation cascade of the immune system is initiated by multivalent binding of its first component, C1q, to the **Fc** region of immunoglobulins in immune complexes. The C1q binding site on mouse IgG2b has been shown to contain the amino acids Glu 318, Lys 320 and Lys 322 in the **CH2 domain** (Duncan, A.R., Winter, G., 1988. The binding site for C1q on IgG. Nature 322 738-740). Identical or closely related motifs are found on all IgGs in all species, and the binding site has therefore been thought to be universal. However, the results from another study indicate that the site is different in human IgG1 molecules (Morgan, A., Jones, N.D., Nesbitt, A.M., et al., 1995. The N-terminal end of the **CH2 domain** of **chimeric** human IgG1 anti-HLA-DR is necessary for C1q, **Fc** gamma RI and **Fc** gamma RIII binding. Immunology 86 319-324). To determine the site(s) responsible for complement activation in anti-NIP-mouse/human IgG3 antibodies, we have mutated amino acids Lys 276, Tyr 278, Asp 280, Glu 318, Lys 320 and Lys 322 in two beta-strands in the **CH2 domains** of human IgG3. In addition, we mutated the Glu 333, which resides in close proximity to the postulated C1q-binding site of mouse IgG2b, as well as Leu 235 in the lower hinge region. All mutants were tested in Antibody Dependent **Complement Mediated Lysis** (ADCML)<sup>4</sup> assays, where the antigen concentration on target cells was varied and human serum was complement source. Only the mutants that lacked the positively charged side chain of lysine in position 322 showed strong reduction in ADCML, particularly at low antigen density on target cells. Alanine scanning of positions 318 and 320 did not affect ADCML, contrary to what was observed for mouse IgG2b. Neither did a leucine to glutamic acid mutation in position 235 have the effect that has been reported for human IgG1. These results suggest that the complement binding site on human IgG3 molecules is different from that found on mouse IgG2b, and possibly on human IgG1 as well. Thus the contact site may not be conserved.

L37 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

1999:736770 Document No. 131:350263 **Chimeric** proteins containing IgG **Fc** fragments which do not trigger **complement mediated lysis**. Armour, Kathryn Lesley; Clark, Michael Ronald; Williamson, Lorna McLeod (Cambridge University Technical Services Limited, UK). PCT Int. Appl. WO 9958572 A1 19991118, 81 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1441 19990507. PRIORITY: GB 1998-9951 19980508.

AB The authors disclose recombinant polypeptides comprising: (i) a binding domain capable of binding a target mol., and (ii) an effector domain having an amino acid sequence substantially homologous to all or part of a constant domain of a human Ig heavy chain. These **chimeric** proteins are capable of binding the target mol. without triggering significant complement dependent lysis, or cell mediated destruction of the target and, via the effector domain, remain capable of specifically binding FcRn and/or **Fc.gamma.RIIb**. These effector domains are derived from two or more human Ig heavy chain **CH2 domains**. The binding domain of the **chimeric** proteins may be derived from antibodies, enzymes, hormones, receptors, and cytokines etc.

=> s (armour k?/au or clark m?/au or williamson l?/au)

L38 13352 (ARMOUR K?/AU OR CLARK M?/AU OR WILLIAMSON L?/AU)



=> s 138 and binding molecule  
L39 1 L38 AND BINDING MOLECULE

=> d 139 cbib abs

L39 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN  
1995:582643 Document No. 122:308083 design of therapeutic mols. having  
binding domain linked to human immunoglobulin heavy chain const. region  
having a particularly desired effector function and use as pharmaceutical.  
**Clark, Michael Ronald** (Lynxvale Ltd., UK). PCT Int. Appl. WO  
9505468 A1 19950223, 46 pp. DESIGNATED STATES: W: GB, JP, US; RW: AT,  
BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English).  
CODEN: PIXXD2. APPLICATION: WO 1994-GB1790 19940816. PRIORITY: GB  
1993-16989 19930816.

AB A **binding mol.** was engineered which has a first amino  
acid sequence comprising a domain with an ability to bind to a target mol.  
and a second amino acid sequence substantially homologous to part of all  
of the constant region of human Ig heavy chain, but which differs in all  
allotypic determinant. The difference in allotypic determinants results  
in the **binding mol.** having an improved effector  
function as compared to a **binding mol.** having the  
first amino acid sequence and part or all of the constant region of the Ig  
heavy chain. In addition method for making a **binding mol.**  
. which has a first amino acid sequence comprising a domain with an  
ability to bind to a target and a second amino acid sequence comprising  
part of all of a human Igs heavy chain having an allotypic determinant of  
a sequence associated with a desired effector function.

=> s 138 and chimer?  
L40 167 L38 AND CHIMER?

=> s 140 and Fc  
L41 21 L40 AND FC

=> s 141 and complement mediated lysis  
L42 1 L41 AND COMPLEMENT MEDIATED LYSIS

=> d 142 cbib abs

L42 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN  
1999:736770 Document No. 131:350263 **Chimeric** proteins containing  
IgG **Fc** fragments which do not trigger **complement**  
**mediated lysis. Armour, Kathryn Lesley;**  
**Clark, Michael Ronald; Williamson, Lorna McLeod**  
(Cambridge University Technical Services Limited, UK). PCT Int. Appl. WO  
9958572 A1 19991118, 81 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD,  
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,  
SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,  
BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY,  
DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE,  
SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1441  
19990507. PRIORITY: GB 1998-9951 19980508.

AB The authors disclose recombinant polypeptides comprising: (i) a binding  
domain capable of binding a target mol., and (ii) an effector domain  
having an amino acid sequence substantially homologous to all or part of a  
constant domain of a human Ig heavy chain. These **chimeric**  
proteins are capable of binding the target mol. without triggering  
significant complement dependent lysis, or cell mediated destruction of  
the target and, via the effector domain, remain capable of specifically

binding FcRn and/or **Fc**.gamma.RIIb. These effector domains are derived from two or more human Ig heavy chain CH2 domains. The binding domain of the **chimeric** proteins may be derived from antibodies, enzymes, hormones, receptors, and cytokines etc.

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PROCESSING COMPLETED FOR L41

L43 15 DUP REMOVE L41 (6 DUPLICATES REMOVED)

=> d l43 1-15 cbib abs

L43 ANSWER 1 OF 15 MEDLINE on STN DUPLICATE 1

2005604331. PubMed ID: 16224816. Function-blocking antibodies to human vascular adhesion protein-1: a potential anti-inflammatory therapy. Kirton Christopher M; Laukkanen Marja-Leena; Nieminen Antti; Merinen Marika; Stolen Craig M; **Armour Kathryn**; Smith David J; Salmi Marko; Jalkanen Sirpa; **Clark Michael R.** (Immunology Division, Department of Pathology, Cambridge University, Cambridge, UK.. mrc7@cam.ac.uk) . European journal of immunology, (2005 Nov) 35 (11) 3119-30. Journal code: 1273201. ISSN: 0014-2980. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Human vascular adhesion protein-1 (VAP-1) is a homodimeric 170-kDa sialoglycoprotein that is expressed on the surface of endothelial cells and functions as a semicarbazide-sensitive amine oxidase and as an adhesion molecule. Blockade of VAP-1 has been shown to reduce leukocyte adhesion and transmigration in in vivo and in vitro models, suggesting that VAP-1 is a potential target for anti-inflammatory therapy. In this study we have constructed mouse-human **chimeric** antibodies by genetic engineering in order to circumvent the potential problems involved in using murine antibodies in man. Our **chimeric** anti-VAP-1 antibodies, which were designed to lack **Fc**-dependent effector functions, bound specifically to cell surface-expressed recombinant human VAP-1 and recognized VAP-1 in different cell types in tonsil. Furthermore, the **chimeric** antibodies prevented leukocyte adhesion and transmigration in vitro and in vivo. Hence, these **chimeric** antibodies have the potential to be used as a new anti-inflammatory therapy.

L43 ANSWER 2 OF 15 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2005:1192373 The Genuine Article (R) Number: 987QC. **Chimeric** human IgG1 anti-idiotypic antibody inhibits basophil degranulation through crosslinking of **Fc** epsilon RI and **Fc** gamma RIIb. Wigginton S J (Reprint); **Armour K L**; **Clark M R**; Sewell H F; Shakib F. Univ Nottingham, Inst Infect Immun & Inflamm, Allergy Res Grp, Nottingham NG7 2RD, England; Univ Cambridge, Dept Pathol, Div Immunol, Cambridge CB2 1QP, England. IMMUNOLOGY (DEC 2005) Vol. 116, Supp. [1], pp. 14-14. ISSN: 0019-2805. Publisher: BLACKWELL PUBLISHING, 9600 GARSINGTON RD, OXFORD OX4 2DQ, OXON, ENGLAND. Language: English.

L43 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN

2003:892819 Document No. 139:380014 Novel humanized anti-VAP-1 monoclonal antibody prepn. and uses thereof. Jalkanen, Sirpa; Salmi, Marko; Laukkanen, Marja-Leena; **Clark, Michael Ronald** (Biotie Therapies Corporation, Finland). PCT Int. Appl. WO 2003093319 A1 20031113, 56 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BF, BJ, BJ, CF, CF, CG, CG, CH, CI, CI, CM, CM, CY, DE, DK, ES, FI, FR, GA, GA, GB, GR, IE, IT, LU, MC,

ML, ML, MR, MR, NE, NE, NL, PT, SE, SN, SN, TD, TD, TG, TG, TR.  
(English). CODEN: PIXXD2. APPLICATION: WO 2003-FI330 20030428.  
PRIORITY: FI 2002-807 20020429.

AB Mouse-human **chimeric** anti-VAP-1 antibodies and fragments thereof are disclosed. Also disclosed are nucleic acids encoding anti-VAP-1 antibodies or fragments thereof, as well as expression vectors and host cells incorporating these nucleic acids for the recombinant expression of anti-VAP-1 antibodies. Pharmaceutical compns. comprising said antibodies and therapeutic uses thereof are also disclosed. In one example, to test the recognition properties of the **chimeric** antibodies in human tissue, tonsil sections were treated with **chimeric** or parental (mouse) antibodies, which resulted in comparable inhibition of lymphocyte binding to high endothelial venules (HEV), indicating that the **chimeric** antibodies have the same function-blocking properties as their murine counterparts; also, the **chimeric** antibodies did not bind to **Fc.gamma.RI** receptors, in contrast to parental antibodies. The effect of the **chimeric** antibody BTT-1002 was assessed in the model of collagen-induced arthritis in the rhesus monkey to determine the usefulness of BTT-1002 in arthritic indications. All examples demonstrate that the **chimeric** anti-VAP-1 antibodies retained the specific recognition patterns of their murine counterparts, lacked human **Fc.gamma.RI** binding activity, blocked the VAP-1-dependent lymphocytes binding to HEV, and were anti-inflammatory.

L43 ANSWER 4 OF 15 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2

2002374739 EMBASE The production and characterisation of a chimaeric human IgE antibody, recognising the major mite allergen Der p 1, and its chimaeric human IgG1 anti-idiotypic. Furtado P.B.; McElveen J.E.; Gough L.; Armour K.L.; Clark M.R.; Sewell H.F.; Shakib F.. Dr. F. Shakib, Div. of Molec./Clinical Immunology, Fac. of Medicine and Health Sciences, Queen's Medical Centre, Nottingham NG7 2UH, United Kingdom. farouk.shakib@nottingham.ac.uk. Journal of Clinical Pathology - Molecular Pathology Vol. 55, No. 5, pp. 315-324 2002.  
Refs: 40.

ISSN: 1366-8714. CODEN: MOPAF6

Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20021107

AB Background: Two mouse monoclonal antibodies have been described, namely: mAb 2C7 (IgG2b $\kappa$ ), which is directed against the major house dust mite allergen Der p 1, and mAb 2G10 (IgG1 $\kappa$ ), which is an anti-idiotypic antibody raised against mAb 2C7. Given its broad IgE specificity, anti-idiotypic mAb 2G10 could potentially have immunomodulatory applications. For example, a chimaeric human IgG version of mAb 2G10 could prove to be a useful molecule for binding to mast cell and basophil **Fc.epsilon.RI** bound IgE, and in doing so co-ligating **Fc.epsilon.RI** with **Fc.gamma.RIIB**, which has been reported to have downregulatory effects. Aims: To produce a chimaeric human IgE version of mAb 2C7 (mAb 2C7huE) and a chimaeric human IgG1 version of its anti-idiotypic mAb 2G10 (mAb 2G10huG1). Methods: The V $\kappa$  and V $H$  regions of mAb 2C7 and its anti-idiotypic mAb 2G10 were engineered into human constant regions of the IgE and IgG1 isotypes, respectively. Results: The production of chimaeric mAb 2C7huE and its anti-idiotypic mAb 2G10huG1 confirmed that the respective mouse antibody V regions were successfully engineered into human constant regions and still retained the specificity of the original murine V regions. Conclusion: The newly constructed chimaeric antibodies will be useful to investigate the downregulation of IgE mediated hypersensitivity by the crosslinking of **Fc.epsilon.RI** with **Fc.gamma.RIIB**.

L43 ANSWER 5 OF 15 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 3

2000276982 EMBASE Antibody humanization: A case of the 'Emperor's new clothes'?. **Clark M.** M. Clark, Immunology Division, Department of Pathology, Cambridge University, Tennis Court Road, Cambridge CB2 1QP, United Kingdom. mrc7@cam.ac.uk. Immunology Today Vol. 21, No. 8, pp. 397-402 2000.

Refs: 42.

ISSN: 0167-5699. CODEN: IMTOD8

S 0167-5699(00)01680-7. Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20000824

AB The antiglobulin response is perceived as a major problem in the clinical development of therapeutic antibodies. Successive technical developments such as **chimeric**, humanized and, now, fully human antibodies claim to offer improved solutions to this problem. Although there is clear evidence that **chimeric** antibodies are less immunogenic than murine monoclonal antibodies, little evidence exists to support claims for further improvements as a result of more elaborate humanization protocols.

L43 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN

1999:736770 Document No. 131:350263 **Chimeric** proteins containing IgG **Fc** fragments which do not trigger complement mediated lysis.

**Armour, Kathryn Lesley; Clark, Michael Ronald;**

**Williamson, Lorna McLeod** (Cambridge University Technical Services Limited, UK). PCT Int. Appl. WO 9958572 A1 19991118, 81 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1441 19990507. PRIORITY: GB 1998-9951 19980508.

AB The authors disclose recombinant polypeptides comprising: (i) a binding domain capable of binding a target mol., and (ii) an effector domain having an amino acid sequence substantially homologous to all or part of a constant domain of a human Ig heavy chain. These **chimeric** proteins are capable of binding the target mol. without triggering significant complement dependent lysis, or cell mediated destruction of the target and, via the effector domain, remain capable of specifically binding FcRn and/or **Fc**.gamma.RIIb. These effector domains are derived from two or more human Ig heavy chain CH2 domains. The binding domain of the **chimeric** proteins may be derived from antibodies, enzymes, hormones, receptors, and cytokines etc.

L43 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN

1998:708959 Document No. 129:329707 **Fc** receptor non-binding anti-CD3 monoclonal antibodies deliver a partial TCR signal and induce clonal anergy. Smith, Judith A.; Tso, J. Yun; **Clark, Marcus R.;** Cole, Michael S.; Bluestone, Jeffrey A. (Arch Development Corporation, USA). PCT Int. Appl. WO 9847531 A2 19981029, 190 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US8029 19980421. PRIORITY: US 1997-44084 19970421.

AB Disclosed are humanized murine anti-CD3 mAbs for use as immunosuppressive agents in clin. transplantation or for treating diseases such as autoimmune diseases, infection, cancer, or immunodeficiency. These humanized antibodies are less toxic and are **Fc** receptor

non-binding anti-CD3 mAb. These **Fc** receptor non-binding anti-CD3 antibodies induces  $\zeta$  chain tyrosine phosphorylation of a p21 form of the TCR complex and triggers ZAP-70 association. These **Fc** receptor non-binding anti-CD3 antibodies were ineffective at inducing the highly phosphorylated form of  $\zeta$  chain p23 form and tyrosine phosphorylation of the associated ZAP-70 tyrosine kinase. This proximal signaling deficiency correlated with minimal PLC $\gamma$ -1 phosphorylation and failure to mobilize detectable Ca<sup>2+</sup>. These **Fc** receptor non-binding anti-CD3 antibodies deliver partial TCR signal and selectively inactivate Th1 and interleukin 2 producing T cell while promoting Th2 type T cells. A bispecific anti-CD3 x anti-CD4 F(ab)'<sub>2</sub> reconstituted early signal transduction events and induced proliferation, suggesting that defective association of lck with the TCR complex may underlie the observed signaling differences between the mitogenic and **Fc** receptor non-binding anti-CD3.

L43 ANSWER 8 OF 15 MEDLINE on STN

97210558. PubMed ID: 9057631. B-cell antigen receptor-induced apoptosis requires both Ig alpha and Ig beta. Tseng J; Eisfelder B J; **Clark M R**. (Department of Medicine, University of Chicago, IL 60637, USA. ) Blood, (1997 Mar 1) 89 (5) 1513-20. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The response of a B cell to antigen is dependent on the surface expression of a clonotypic B-cell receptor complex (BCR) consisting of membrane-bound Ig and disulfide-linked heterodimers of Ig alpha/beta. Studies of Ig alpha or Ig beta have shown that the immunoreceptor tyrosine-based activation motif (ITAM) found in each cytoplasmic tail is capable of inducing most receptor signaling events. However, Ig alpha, Ig beta, and most of the other receptor chains that contain ITAMs, including CD3 epsilon, CD3 gamma, TCR zeta, and **Fc** epsilon R1 gamma, are found as components of multimeric and heterogeneous complexes. In such a complex it is possible that cooperativity between individual chains imparts functional capacities to the intact receptor that are not predicted from the properties of its constituents. Therefore, we developed a novel system in which we could form and then aggregate dimers, representative of partial receptor complexes, which contained either Ig alpha alone, Ig beta alone, or the two chains together and then examine their ability to induce apoptosis in the immature B-cell line, WEHI-231. Here we present evidence that heterodimers of Ig alpha and Ig beta efficiently induced apoptosis while homodimers of either chain did not. Apoptosis was associated with the inductive tyrosine phosphorylation of a very restricted set of proteins including the tyrosine kinase Syk. These findings may provide insight into the mechanisms by which the BCR, and other such multimeric receptor complexes, initiate both apoptotic and proliferative responses to antigen.

L43 ANSWER 9 OF 15 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1997:148883 The Genuine Article (R) Number: BH16J. IgG effector mechanisms.

**Clark M R (Reprint)**. UNIV CAMBRIDGE, DEPT PATHOL, DIV IMMUNOL, CAMBRIDGE CB2 1TN, ENGLAND (Reprint). ANTIBODY ENGINEERING (1997) Vol. 65, pp. 88-110. ISSN: 1015-0145. Publisher: KARGER, POSTFACH, CH-4009 BASEL, SWITZERLAND. Language: English.

L43 ANSWER 10 OF 15 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1995:111533 The Genuine Article (R) Number: QG208. INTERACTION OF HUMAN

MONOCYTE **FC**-GAMMA RECEPTORS WITH RAT IGG2B - A NEW INDICATOR FOR THE **FC**-GAMMA-RIIA (R-H131) POLYMORPHISM. HAAGEN I A (Reprint); GEERARS A J G; **CLARK M R**; VANDEWINKEL J G J. UNIV UTRECHT HOSP, DEPT IMMUNOL F03821, POSTBOX 85500, 3508 GA UTRECHT, NETHERLANDS (Reprint); UNIV CAMBRIDGE, DEPT PATHOL, CAMBRIDGE, ENGLAND. JOURNAL OF IMMUNOLOGY (15 FEB 1995) Vol. 154, No. 4, pp. 1852-1860. ISSN: 0022-1767.

Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Rat mAbs receive considerable interest for immunologic intervention in man. The rat IgG2b isotype has previously been found to be optimally active both in vivo and in vitro. We found that both a rat IgG2b CD3 mAb and a monovalent hybrid rat IgG2b-mouse IgG1 bispecific Ab triggered T cell activation in PBMC. Inhibition analyses with mAb blocking different human IgG Fc receptors (Fc gamma R) showed a dimorphic pattern. In donors expressing an Fc gamma RIIa-R/R131 allotype (previously defined on the basis of interaction with mouse (m) IgG1 as 'high responder') anti-Fc gamma RI mAb 197 inhibited rat IgG2b induced T cell mitogenesis almost completely. In Fc gamma RIIa-H/H131 ('low responder' allotype) donors, however, both anti-Fc gamma RI mAb 197 and anti-Fc gamma RII mAb IV.3 were essential for optimal inhibition of mitogenesis. T cell proliferation experiments performed with the use of Fc gamma R-transfected fibroblasts as accessory cells showed the high affinity Fc gamma RIa (CD64) to interact with both rat IgG2b and rat IgG2b-mlgG1 hybrid CD3 mAb. The use of the two types of Fc gamma RIIa (CD32)-transfectants instead showed rat IgG2b CD3 mAb to interact solely with the IIa-H/H131 allotype. Interestingly, rat IgG2b-mlgG1 hybrid mAb did not interact effectively with this low affinity Fc gamma R. This suggests a requirement for only one rat IgG2b H chain for Fc gamma RIa-mediated binding, whereas two identical H chains seem to be necessary for proper interaction with Fc gamma RIIa. Ab-sensitized RBC-rosette experiments performed with the use of a rat IgG2b anti-NIP mAb confirmed the interaction pattern observed with rat CD3 mAb, supporting the phenomena to be isotype-, and not mAb-, dependent. These analyses point to a unique reactivity pattern for rat IgG2b Abs, interacting both with the high affinity Fc gamma RIa in all donors and Fc gamma RIIa of individuals expressing the IIa-H131 allotype.

L43 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN

1995:96590 Document No. 122:158106 Humanized antibodies specific for human cancers. Wallace, P.; **Armour, K.**; Carr, F.; Fitzek, M.; King, S.; Steven, J.; Kitamura, K.; Rettig, W.; Richards, E.; et al. (Res. Center, Scotgen Biopharmaceuticals Inc., Aberdeen, AB22 8GU, UK). Conf. Ind. Immunol., Two-Day Symp., 2nd, 52-4. Inst. Chem. Eng.: Rugby, UK. (English) 1994. CODEN: 60NTAU.

AB The use of murine antibodies as in vivo diagnostic and therapeutic agents is limited by their short half-life in human serum, by the adverse HAMA response and by poor Fc-dependent stimulation of human effector functions. To overcome these deficiencies murine antibodies can be converted to humanized antibodies by the application of recombinant DNA technol. Here the authors describe how two antibodies have been humanized using Scotgen's 'fixed framework/minimal modification' adaptation of CDR-grafting technol. Furthermore the authors identify four regions within the V regions (but outside the CDRs) that can be of particular importance for the retention of antigen binding specificity and efficacy.

L43 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN

1994:29350 Document No. 120:29350 Anti-CD3 aglycosylated IgG antibody. Bolt, Sarah Louise; **Clark, Michael Ronald**; Gorman, Scott David; Routledge, Edward Graham; Waldmann, Herman (UK). PCT Int. Appl. WO 9319196 A1 19930930, 41 pp. DESIGNATED STATES: W: AU, CA, JP, KR, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1992-GB1933 19921021. PRIORITY: GB 1992-6422 19920324.

AB Recombinant humanized IgG antibodies to human CD3 antigen are provided which retain their antigen-binding specificities and immunosuppressive properties and yet do not induce T-cell mitogenesis in vitro, induce a

reduced level of cytokine release in vivo, and maintain some **Fc** binding ability. The antibodies may be useful for immunosuppression, e.g. in transplant recipients, or for treatment of cancer. Thus, the variable regions of the heavy and  $\lambda$  light chain genes of rat anti-human CD3 antibody YTH 12.5 were cloned and reshaped by site-directed mutagenesis, and ligated with genes for human IgG1 constant regions. Substitution of Asn with Ala prevented glycosylation of the antibody during expression by CHO cells. The **chimeric** aglycosylated antibody blocked the mixed lymphocyte reaction, indicating that it had a reduced capacity to interact with **Fc** receptors on accessory cells, and induced less release of tumor necrosis factor in human CD3 transgenic mice than did the parental IgG1 antibody.

L43 ANSWER 13 OF 15 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

93120172 EMBASE Document No.: 1993120172. Structural motifs involved in human IgG antibody effector functions. Greenwood J.; **Clark M.**; Waldmann H.. Dept of Pathology (Immunology Div), Tennis Court Road, Cambridge CB2 1QP, United Kingdom. European Journal of Immunology Vol. 23, No. 5, pp. 1098-1104 1993. ISSN: 0014-2980. CODEN: EJIMAF

Pub. Country: Germany. Language: English. Summary Language: English.  
ED Entered STN: 930530

AB A humanized IgG antibody to CAMPATH-1 antigen (CDw52) is known to be lympholytic both in vitro and in vivo. So as to improve therapeutic potency through protein engineering strategies, we wish to define the structural motifs underlying some of the documented differences in function between human (h) IgG1 and IgG4 forms of the antibody. By the creation of heavy chain domain-switch and intra-domain recombinant antibodies we have established an important role for the carboxy-terminal half of the CH2 domain in determining differential behaviour in antibody-dependent cytotoxicity (ADCC) and in complement lysis. If this same region were necessary for the effector mechanisms that operate in vivo, then it might be possible to improve antibody effector functions by construction of novel antibodies that possess within the one molecule multiple copies of the crucial hinge-CH2 associated structures. Although our previous work suggested that the hIgG4 CAMPATH-1 antibody was ineffective at ADCC, we found this to be so only in some individuals. In others, IgG4, and indeed all the IgG subclasses were able to mediate ADCC. Overall, though, hIgG1 remains the best choice isotype for lytic therapy in vivo.

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1994:455264 Document No. 121:55264 Chemically engineered **chimeric** and multi-Fab antibodies. Stevenson, G. T.; Glennie, M. J.; Kan, K. S. (Tenovus Res. Lab., Southampton Univ. Hosp., Southampton, SO9 4XY, UK). Protein Eng. Antibody Mol. Prophyl. Ther. Appl. Man, 127-41. Editor(s): **Clark, Mike**. Academic Titles: Nottingham, UK. (English) 1993. CODEN: 59ZGAX.

AB A review, with 27 refs., discussing sulfur chemical of Ig mols., the derivation of Fab fragments from monoclonal antibodies, selective closure of the  $\gamma$ -light chain disulfide bond in Fab fragments, selection of univalent vs. multivalent antibodies for the target epitope, and **Fc**-containing derivs.

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89215277. PubMed ID: 2496159. A matched set of rat/mouse **chimeric** antibodies. Identification and biological properties of rat H chain constant regions  $\mu$ ,  $\gamma$  1,  $\gamma$  2a,  $\gamma$  2b,  $\gamma$  2c,  $\epsilon$ , and  $\alpha$ . Bruggemann M; Teale C; **Clark M**; Bindon C; Waldmann H. (Department of Pathology, University of Cambridge, England. ) Journal of immunology (Baltimore, Md. : 1950), (1989 May 1) 142 (9) 3145-50. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language:

English.

AB Rat C regions mu, gamma 1, gamma 2a, gamma 2b, gamma 2c, epsilon, and alpha have been characterized by means of **chimeric** antibody technology. A set of rat/mouse Ag-specific (anti-4-hydroxy-3-nitrophenacetyl) antibodies was constructed that differ only in the H chain constant region but carry identical V region and L chain, both of which are of mouse origin. All rat constant regions could be expressed and m.w. were as expected from the protein sequence. A slight variation in mobility within the IgG subclasses allowed us to establish a hierarchy for the sizes of the four gamma H chains; gamma 2b greater than gamma 1 greater than gamma 2c greater than gamma 2a. Rat IgG2c and IgG2b could be purified on both protein A and protein G while rat IgG2a could only be purified on protein G. Rat IgM and IgG2b were the most potent in C-mediated hemolysis. This was not simply a consequence of the amount of Clq bound because IgG2c bound Clq efficiently but was relatively poor in cell lysis. In ADCC using human effector and target cells, IgG2b and IgG1 were the most effective.

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